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CANCER RESEARCH

PROJECTS FUNDED UNDER THE SIXTH FRAMEWORK PROGRAMME

2002-2006

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CANCER RESEARCH

PROJECTS FUNDED UNDER THE SIXTH FRAMEWORK PROGRAMME (2002-2006)

Edited by ELENGO MANOUSSAKI

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Elengo Manoussaki

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CANCER: COMBATING A COMPLEX DISEASE

Human cancer is one of the oldest documented diseases. The oldest written evidence of the disease is found in Egyptian papyri from the period 3000 to 1500 BC which describe ulcers and breast cancer. The oldest specimen is a bronze age (1900-1600 BC) female skull suggesting head and neck cancer, whereas skeletal remains of a Peruvian – INCA – woman suggest melanoma.

Breast cancer, melanoma, as well as head and neck cancer and other solid cancers, are still present across the world today. Cancer is an increasingly important health burden, both for patients and public health systems with significant societal and psychological consequences.

In recognition of this, a global effort to fight and control cancer has been set. Recently, the European Parliament published a resolution on Combating cancer in the enlarged Europe (1) and the council of the European Union in its conclusions on reducing the burden on cancer (2), invited the European Commission to extend knowledge of cancer epidemiology and cancer risk factors, early detection, diagnosis, treatment, survival and palliative care, as well as to include translational research under the Seventh Framework Programme.

In addition, the World cancer declaration 2008, calls for a concerted strategic action to reduce the global cancer burden and outlines the steps needed to begin to reverse the global cancer crisis by 2020. Moreover, it sets specific priority actions on health policy, prevention and early detection, cancer treatment, and cancer research (3).

The European Union's strong research community is well placed to advance the understanding and treatment of cancer. Traditional approaches such as surgery, radiotherapy and chemotherapy are constantly improving, whilst genomic and immunological research offer innovative prospects for future treatment. In addition, new screening and detection methods are making it possible to confront the disease at an increasingly early stage. Furthermore, palliative care is increasingly recognised as important in ensuring cancer patients and their families to receive the best possible care and quality of life.

The European Union supports cancer research in order to prevent cancer and to improve patients' survival chances and their quality of life. The *'Combating Cancer'* initiative was part of the EU's Combating Major Diseases research. Within the 'Life Sciences, Genomics and Biotechnology for Health' thematic priority of the Sixth Framework Programme, 2002-2006 some € 480 million of funding for cancer research has been made available to the European research community through the programme.

It aimed to combat cancer by developing improved patient-oriented strategies, from prevention to earlier and more effective diagnosis, to better treatment with minimal side effects. It supported initiatives aimed at translating knowledge of basic research into applications to improve clinical practice and public health actions.

This distinctive patient-oriented approach included four interlinked components, focusing on:

- Establishing facilities and developing initiatives for the exploitation of cancer research in Europe, encouraging the development of evidence-based guidelines for good clinical practice and improved public health strategies by accelerating the translation of existing research results into applications.

(1) http://www.europarl.europa.eu/sides/getDoc.do?pubRef=-//EP//NONSGML+TA+P6-TA-2008-0121+0+DOC+WORD+V0//EN
(2) Adopted 10/06/08, www.consilium.europa.eu/Newsroom
(3) http://www.uicc.org/wcd/wcd2008.pdf

- Supporting clinical research, particularly early stage (phase I and II) clinical trials, targeted at validating new and improved interventions.
- Funding translational research that takes basic knowledge through to applications in clinical practice and public health.
- Other cancer related issues, such as ageing and cancer, gender related cancer; regional differences, psycho-social aspects, palliative care, and guidance for support groups.

During the lifetime of FP6, many research groups applied and 108 projects were selected for funding. Among the funded ones are 37 large Integrated Projects (IP) or Networks of Excellence (NoE); 64 Specific Targeted Research Projects (STREP) and 7 Coordination or Support Actions (CSA).

The EU is committed to funding excellence in European biomedical research. All submitted proposals were subject to a rigorous, transparent and equitable peer-reviewed evaluation carried out by independent international panels of high-level experts from academia, public and private research organisations, and industry.

Connecting European academic excellence with innovative research-based industry is the key to the success of translational research. Therefore, the Commission particularly encouraged small and medium-sized enterprises (SME) to participate in its research programmes.

The present catalogue includes cancer projects on a variety of topics. No less than 1 500 research teams are collaborating in European Union Member States and other European countries associated with the Framework Programme, as well as selected third countries, such as USA, Chile, Australia, Russian Federation etc., thus consolidating an important critical mass to fight cancer. In fact, virtually all major European cancer research centres are taking part in one or several of the Commission-funded support schemes.

The presentation of the catalogue follows the Common Scientific Outline (CSO) first presented as a classification system of scientific interest in cancer research, in the framework of the Cancer Research Portfolio (CRP) of the National Institute of Health, USA.

They include 7 broadly defined research areas:
- Biology
- Aetiology (causes of cancer)
- Prevention
- Early detection, diagnosis and prognosis
- Treatment
- Cancer control, survivorship and outcomes research
- Scientific model systems

The division into the different groups is not always straightforward; therefore some of the projects could be classified in one or more of the above areas. The essential fact is that these projects are all present in the catalogue and represent the enormous effort and constant devotion of the European research society to fight cancer.

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Biology

Cancer is a disease that is characterized by uncontrolled growth and spread of abnormal cells. Transformation of a normal cell into a cancer cell is a complex multistep process in which cells acquire capabilities to divide indefinitely independently of growth signals, evade programmed cell death, invade neighbouring tissues and metastasise to other parts of the body. During this transformation numerous changes occur at the molecular, biochemical and cellular level. All cancers arise due to accumulation of genetic and epigenetic changes. Some mutations may be present in the germline thus increasing the risk of cancer development, but many occur during the individual's life in the somatic cells. There are many aetiological factors involved in cancer, including infection, exposure to chemicals and other environmental risk factors and heredity. The past years have witnessed a dramatic progress in understanding the mechanisms of transformation of a normal cell into a cancer cell that is expected to lead to major improvements in therapy. Yet, our knowledge is still far from complete and much remains to be discovered.

Thirty six projects presented in this section investigate mechanisms that underlie cancer initiation, progression and metastasis and compare them with their normal counterparts. A number of them focus on molecular mechanisms, including DNA repair, oncogenes, tumor suppressor genes, chromosome alterations, telomere maintenance, epigenetics, and programmed cell death.

Due to availability of the complete human genome and rapid increase in proteomic and transcriptomic data an integrative approach is needed. A group of projects presented in this section employ systems and computational biology approaches and high-throughput analyses to investigate complex network of interactions in the cell.

Moreover, FP6 supports research on the development of sophisticated tools and novel technologies, for example analyses and imaging in situ, that will enable researchers to investigate normal functioning of the cell and the changes that lead to cancer initiation and progression.

'Know your enemy' – said Sun Tzu in the 'The Art of War'. Research on cancer biology is crucial in our fight with cancer. Exploring the key genetic, biochemical and cellular changes involved in cancer initiation and progression will yield new disease biomarkers and targets for treatment and ultimately pave the way to new therapies.

Dominika Trzaska

Keywords | Tumour suppression | p53 | p73 | p63 | inhibitors | activators |

Active p53

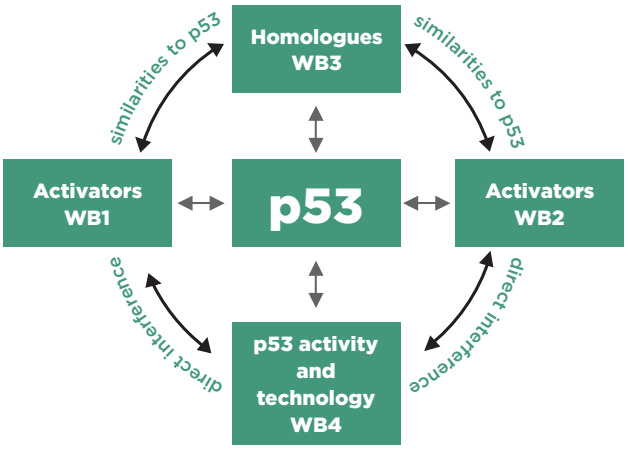
Manipulating tumour suppression: a key to improve cancer treatment

Summary

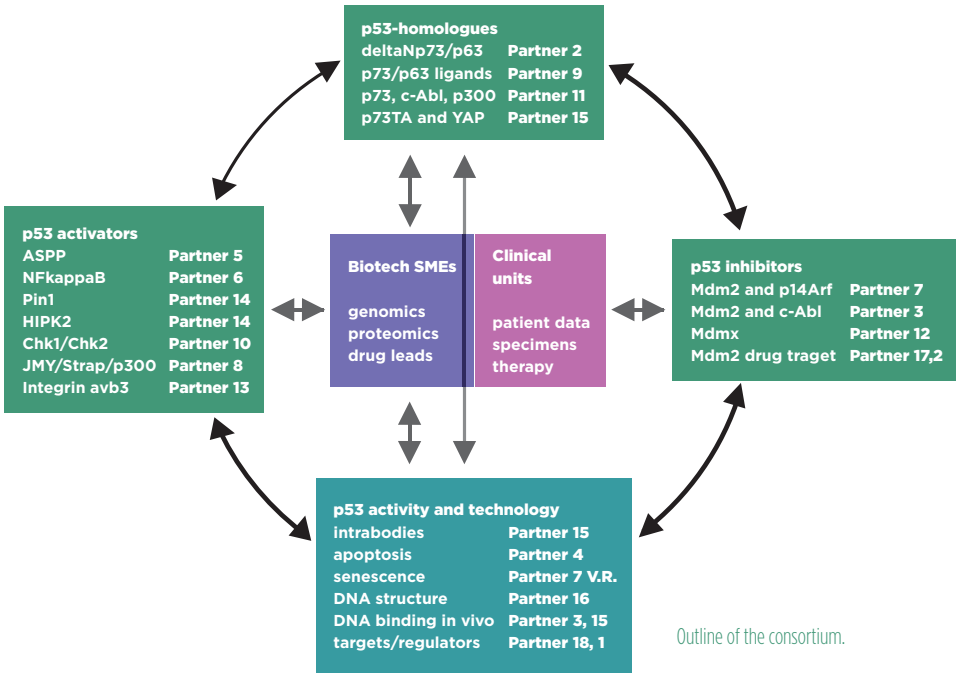
The prevention of human cancer development depends on the integrity of a complex network of defence mechanisms that help cells to respond to various stress conditions. A key player in this network is the p53 tumour suppressor protein. By inducing efficient growth inhibition, p53 eliminates cancer cells thereby preventing the development of human malignancies. These functions of p53 often determine the efficacy of anti-cancer therapies. Although p53 is frequently mutated in some cancers, in about 50 % of all human cancers p53 is non-mutated and could, in principle, be activated to prevent tumour progression. This situation is prevalent among a wide range of cancers, notably breast carcinoma. However, p53 activity is hampered by malfunction of its many modulators, such as Mdm2 or p73, which govern p53 tumour suppressive activity by acting upstream and/or downstream of p53. There is therefore a crucial need to understand how p53 modulators contribute to human malignancies. Based on this information, we propose to develop rational therapeutic approaches to manipulate p53 modulators, thereby wakening the sleeping tumour suppression activities of p53, allowing it to eliminate cancer cells. This carefully structured consortium comprising 20 academic research centres and SMEs (see diagram) will interactively build a technology platform to comparatively identify, characterise and evaluate the regulatory roles of p53 modulators and define the mechanisms of their action. Large-scale gene functional analyses will be conducted to identify relevant signalling pathways that impair or mediate tumour suppression by p53. These analyses will include p53 activators and inhibitors, p53 homologues p73/p63, and dissection of p53 target genes mediating apoptosis and growth arrest. Our links with highly profiled clinical partners and our access to large, well-characterised and clinically documented sample collections will enable the evaluation of diagnostic expression profiles, and their potential prognosis value in cancer. Particular emphasis will be directed towards translating the information on p53 regulation into the development of new anti-cancer therapies. p53 regulatory proteins will be used for the identification of new molecular targets for drug discovery.

Problem

Cancer is the second leading cause of death in European countries, and one of the most imminent health problems in the developed world. The p53 protein is generally recognised as the key determinant of tumour suppression. It has been declared by the European Union that 'a large co-operative effort is needed to ensure that every European citizen will rapidly profit from the revolution of knowledge in cancer management' (Philippe Busquin). The presence of wild type p53 is particularly prevalent in breast cancer, the type of cancer that stands at the centre of the European cancer policy. Since breast cancer affects mostly (though not exclusively) women, breast cancer research is also an important task to implement the gender dimension into basic research. For these reasons, we will choose breast cancer as one of our focuses in this block of work. Moreover, a non-mutated but inactive p53 is also found in a high percentage of the most frequent intracranial tumour of children, neuroblastoma. Since paediatric tumours are particularly dramatic events for patients and their families, it appears appropriate to put another focus on this tumour species.



The four blocks are linked as outlined. These links are formed according to the biological activities governing p53 and, therefore, the scheme simultaneously depicts biological dependencies as well as the mode of collaboration within the consortium. Activators of p53 frequently act by antagonising p53 inhibitors, and vice versa; this will be taken into account by networking accordingly between the blocks 1 and 2. Activators and inhibitors of p53 may act on p73 and p63 as well and this was shown to be true in a number of cases. Therefore, each regulator of p53 will be assessed regarding its impact on p53-homologues as well by collaborative efforts between block of work 3 with blocks 1 and 2. Finally, the assessment of p53 downstream activities, and the development of cutting-edge technologies to analyse them, will be used throughout the consortium. Therefore, block of work 4 forms a basis not only for reaching excellence on its own, but also to effectively advance the progress of blocks 1, 2 and 3.



Outline of the consortium.

Aim

The principal aim of this proposal is to ease both diagnosis and prognostic classification, as well as the efforts towards novel therapy regimens to treat patients suffering from breast cancer and neuroblastoma. Overall, the integrated action of our consortium is aiming at re-establishing tumour suppressor activity in cancer, thereby translating basic knowledge of functional oncogenomics into cancer diagnoses and treatment, and contributing to leadership in European health technology.

Expected results

The overall goals of this integrated effort are to understand:

- which modulators determine the tumour-suppressive activities of the p53 family members;
- by what mechanisms these modulators affect the tumour suppression activities;
- how the expression and activity of p53 modulators is regulated;
- whether p53 modulators affect the biological characteristics of tumour cells;
- whether the status of p53 modulators correlates with the clinical outcome and can be used to determine the individual prognosis;
- whether and how p53 modulators can be targeted by therapeutic strategies, and be manipulated towards regaining tumour suppression;
- disseminate the knowledge that will be produced to practically all the interested parties including medical doctors, and managerial staff in the industries;
- familiarise SMEs with scientific research work and state-of-the art technology that will provide the necessary know-how for the improvement of their services and competitiveness.

Potential applications

The ultimate general objective of this research proposal is to provide a basis for the re-activation of tumour suppression and the design of novel therapeutic approaches to combat cancer. In particular, we are aiming at modulating p53 family activities to decrease resistance of tumour cells to anti-cancer treatments. Thus, the ultimate goal of this research proposal is the identification of novel drug targets and strategies for induction of p53-mediated apoptosis in therapy-resistant cancer cells. The participation of the SMEs is expected to play a key role to the practical application of the knowledge that will be produced.

Project number
LSHC-CT-2004-503576

EC contribution
€ 6 000 000

Duration
60 months

Starting date
01/12/2004

Instrument
IP

Project website
www.europeire.it/Activep53/intro.htm

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Keywords | Angiogenesis | vasculogenesis | blood vessels | tumour | endothelial cells | clinical trials | microarrays | proteomics molecular targets |

ANGIOTARGETING

Multidisciplinary research to explore and validate molecular targets for innovative treatments

Summary

Solid tumour growth depends on the recruitment of new blood vessels that will provide the cancer cells with nutrients and oxygen. The ANGIOTARGETING project intends to find new targets on the tumour vasculature. The project will then define these targets and develop new therapeutic strategies towards them.

The apparent limited success in translating angiogenesis research into the clinic is, in our view, based on the fact that the research field has been fragmented, and no standardised tools and models have been identified that reliably reflect the complexity of tumour angiogenesis mechanisms in humans.

ANGIOTARGETING will identify and validate new therapeutic targets directed towards tumour vascular-matrix interactions, develop new therapeutic strategies and implement such strategies in pre- and clinical trials. The project represents a virtual research institute in Europe and consists of 14 highly competent research centres within the field of angiogenesis research. To define and validate new targets related to the tumour vascular transcriptome and proteome, the consortium will establish high throughput functional screening technologies for the identification of novel secreted factors that regulate endothelial cell growth and survival. This includes the use of robotic platforms that will be used to identify cDNAs with specific cellular functions. In this project, basic science, translational research and clinical activities are strongly integrated, in order to validate defined targets and to develop new therapeutic principles for clinical implementation.

Problem

The significant role of neovessel formation in health and disease has been clearly demonstrated during the last decade. The molecular mechanisms that lead to the establishment of functional blood vessels are also key factors that regulate tumour progression. Considerable efforts have been devoted to research identifying the mechanisms that regulate the recruitment of blood vessels to tumours. Under normal conditions, the establishment of blood vessels is a highly complex and coordinated biological process.

Targeting non-cancer cells that feed and drain the tumour and form channels through which tumour cells can disseminate, rather than targeting the neoplastic cells themselves, represents an approach to cancer therapy that holds particular promise because these cells are genetically stable, and therefore less likely to accumulate mutations that allow them to develop drug resistance. The first meaningful clinical effects of antiangiogenic therapy in human cancer have recently been demonstrated. However, in spite of some highly encouraging results, most angiogenesis inhibitors, reported to suppress tumour growth in animal models, have thus far failed in human clinical trials. In our view, this reflects that no standardised tools and models have been identified that reliably reflect the complexity of tumour angiogenesis mechanisms in humans. The successful translation of potential angiogenesis inhibitors to clinical application depends partly on the transfer of expertise from scientists who are familiar with the biology of angiogenesis to clinicians, as well as an active feedback from the clinicians to the scientists.

ANGIOTARGETING aims at the identification and validation of new therapeutic targets in tumour vasculature, develops new therapeutic strategies and implement such strategies in pre- and clinical trials. A strong focus on translational research and clinical implementation will convert R&D results into direct public and economic benefits.

Aim

The objective is the identification and validation of new therapeutic targets directed towards tumour vascular-matrix interactions.

Expected results

- The project will increase our understanding of how tumours generate a vascular supply.
- The project will develop new technologies to define and validate key molecular targets that control tumour vascularisation and invasion.
- The project will identify potential therapeutic targets towards the tumour vascular and invasive transcriptome and proteome.
- The project will develop comprehensive bioinformatics tools for the analysis of high throughput gene and protein data from defined cell populations within tumours.
- The project will develop state-of-the-art platforms for preclinical and clinical assessment of newly developed compounds.
- The project will provide new information on how potential antivascular therapies shall be evaluated in the clinic. This includes the development of surrogate markers to evaluate therapeutic efficacy.

Project number
LSHC-CT-2004-504743

EC contribution
€ 6 000 000

Duration
54 months

Starting date
01/11/2004

Instrument
IP

Project website
www.uib.no/med/angiotargeting/

Potential applications

The project will lead to the identification of a number of potential targets towards the tumour vasculature. Within the ANGIOTARGETING consortium there are a number of activities aiming at developing novel therapeutic strategies towards identified and validated targets. Some of these strategies will be applied and assessed in preclinical and clinical trials.

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Keywords | Tumour-host interactions | tumour targeting |

Anti-tumour targeting

Modulation of the Recruitment of the Vessels and Immune Cells by Malignant Tumours: Targeting of Tumour Vessels and Triggering of Anti-Tumour Defence Mechanisms

Summary

All malignant tumours acquire the capacity for efficient recruitment of blood vessels, which are absolutely necessary for tumour growth beyond a certain size. They also frequently stimulate lymphangiogenesis supporting dissemination of tumour cells, not only via the blood vasculature but also via the lymphatic system, leading to metastasis. Vessel growth is promoted by sprouting angiogenesis and the homing of bone marrow progenitor cells into the tumours and tumour vessels. The extensive vascularisation facilitates the invasion of cells of the innate and adaptive immune system, which stay largely functionally suppressed by the tumour environment, and even contribute to angiogenesis and tumour growth by cytokine and growth factor secretion.

We propose in this application to:

- further investigate key regulatory pathways by which tumour-secreted molecules promote vascularisation and inhibit immune cell function;
- develop methods to inhibit tumour growth and metastasis by blocking vessel and tumour cell growth;
- achieve tumour clearance by additionally promoting activation and homing of functional immune cells to the tumours.

The project will comprise the collaboration of laboratories with complementary expertise. It will include experts in blood vessel and lymph vessel angiogenesis, metastasis formation, progenitor cell incorporation into tumours and tumour vessels, anti-tumour defence mechanisms of the immune system and viral transduction techniques. The final goal will be the preclinical evaluation of strategies in murine models of three of the most prevalent forms of human cancer, i.e. carcinomas of the breast, colon and prostate.

The strategies to target the tumour will be based on gene, cell and immune therapy methods. They will include the use of:

- adenoviruses for the expression of angiogenesis inhibitors following targeted delivery of the viruses to the tumour vasculature;
- the genetic modification of murine embryonic and human umbilical cord/bone marrow progenitor cells and their directed homing into the tumour;
- the use of genetically-engineered immune cell products or the transduction of immune cells to activate targeting of the tumours by innate and adaptive anti-tumour defence mechanisms. We expect that this project will contribute to innovation on three levels. Firstly, we will gain basic additional novel knowledge on important pathways and regulatory molecules for the recruitment of host cells to the tumours and their functional interaction with the tumour. Secondly, we will use this knowledge to test novel ways of targeting viruses and (transduced) cells to the tumours. Finally, we will evaluate whether, by a combination of anti-angiogenesis therapy with directed anti-tumour immunotherapy, it would be possible not only to inhibit tumour growth, but also to eradicate residual disease.

Problem

Despite significant improvements in diagnosis, surgical techniques, general patient care, and local and systemic adjuvant therapies, many solid tumours remain a major cause of death. Among the most prevalent and fatal forms are carcinomas of the breast, colon and prostate. Most deaths from cancer are due to metastases, seeded from the primary tumour via the blood and lymph vasculature, which are resistant to conventional therapies. The main barrier to the non-surgical treatment of the primary neoplasm and its metastases is the genetic instability and biological heterogeneity of cancer cells leading to the rapid development and growth of resistant cells. Since the expansion of solid tumours and their metastases beyond a minimal size is absolutely dependent on the formation of new blood vessels, anti-angiogenesis therapies constitute a promising alternative. In this case the genetically normal endothelial cells of the tumour vessels are targeted, avoiding the problem of resistance development. Furthermore, immune therapies are based on the ability of the immune system, evolved over evolutionary times, to cope with an almost unlimited number of antigens, thus opening the possibility to find a mechanism to target any tumour variant as long as the inhibitory milieu of the tumour environment can be overcome. Therefore angiogenesis and immune therapies remain among the most promising fields of cancer therapy.

Project number
LSHC-CT-2005-518178

EC contribution
€ 3 005 000

Duration
36 months

Starting date
01/11/2005

Instrument
STREP

Project website
www.tumortargeting.eu

Aim

The general aim of the project is to design and evaluate strategies of anti-tumour angiogenesis and anti-tumour immune therapies and their combination in murine models of some of the most prevalent forms of human solid tumours. It will include the identification, modification and use of key regulatory molecules of vessel growth and immune defence and the development of methods to specifically and efficiently target tumours and their metastasis.

Expected results

We will undertake a concentrated effort to identify targets and develop methods for interference with vessel growth. Furthermore, we will develop techniques to target tumour endothelium by viruses and progenitor cells,methodsthat could be usedto also reachdistant metastases via the blood stream and not only the primary tumour. In addition, we will explore the use of innate receptors of NK cells to detect malignant cells and to boost the T-cell response of the immune system with the help of dendritic cells. Weanticipate thatasingle method,depending on the individual tumour, may not be sufficient, but the development of several techniques based on different principles and their tumour-specific or combined application may be successful.

For this purpose we combine laboratories with differential expertise, each having either identified a specific target molecule or developed a specific technique for targeting tumours. We will combine the expertise, molecules and techniques and comparatively evaluate different strategies in corresponding models of human carcinomas.

Potential applications

The results of this project will be disseminated and exploited on three levels:

- basic molecular medicine research level: all expected findings with the angiogenesis inhibitors and immune stimulators will be important to improve understanding of the role of vessel formation and of anti-tumour immune responses for cancer. These basic findings will be published in quality scientific journals;
- clinical level: it is anticipated that our findings and developed preclinical methods will have impact on the design and further development of clinical protocols for the treatment of cancer;
- company level: key novel molecules, findings and techniques will be patented and, together with patents available, used to develop reagents and protocol for gene-therapy of solid tumours.

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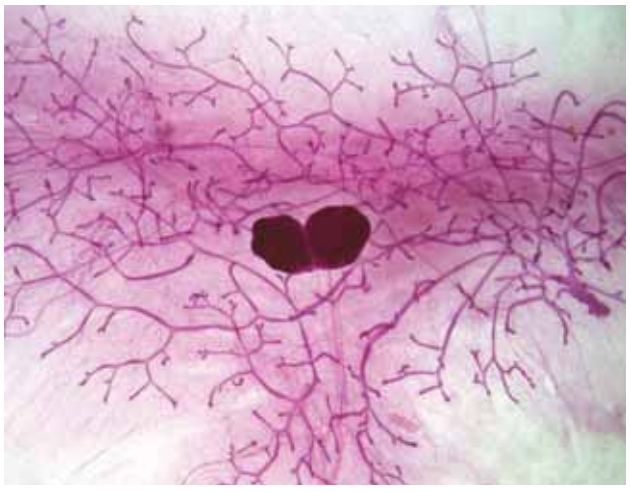
Keywords | Breast | metastasis | gene expression profiling |

BRECOSM

Identification of molecular pathways that regulate the organ-specific metastasis of breast cancer

Summary

The objectives of this project are to identify genes, proteins and molecular pathways involved in regulating the metastasis of breast cancer to specific organs. To achieve these objectives we will use a combination of gene expression profiling, bioinformatic analysis, histology of human female breast cancer samples, genetic manipulation of transplantable tumor cells and transgenic mouse technology. In addition to finding new genes, we aim to analyse to what extent genes already known to play a role in breast cancer metastasis specify which organs breast tumors metastasise to. We will also establish how the currently known genes that are associated with breast cancer dissemination and the new ones we identify fit together into pathways that regulate organ-specific metastasis. These findings will be coupled with the analysis of clinical trials in which participants in this consortium are involved. Further deliverables include the development of improved animal models for the study of breast cancer metastasis, and the development of diagnostic methods for determining whether primary tumours already have metastatic potential. Together, the work packages in this project will establish a pipeline of activities that unite basic research into the organspecific metastasis of breast cancer with target validation and clinical application.



Wholemount staining of the epithelial ductal structure in a mouse mammary gland. The lymph nodes are also visible as densely-stained spheroidal structures.

Problem

Breast cancer is a major health issue and is highly gender relevant. It is the most often diagnosed female cancer, and the majority of cases are already invasive at diagnosis. More than 17% of cancer deaths result from breast tumours, making breast cancer a major societal problem. Treatment involves radical and disfiguring surgery, often with long-term side effects such as the development of lymphedema of the arm, and radiotherapy and chemotherapy, again associated with severe side effects. The effects of metastatic spread of the tumour cells and the formation of secondary deposits in a wide variety of organs are the cause of death due to breast cancer. Metastases to organs such as bone and brain are major causes of suffering in terminally ill patients.

The incidence of breast cancer increases sharply between the ages of 30 and 50 meaning that many women in the prime of life are affected by this disease. Not only does this mean that many families are traumatised, but it also has severe economic consequences, removing economically active women from society. Further economic consequences arise as a result of the high health care costs associated with treating breast cancer patients.

Clearly improvements in the treatment and management of breast cancer would have impact on both health and the economy. By analysing molecular mechanisms that regulate organ-specific metastasis in breast cancer, the BRECOSM project will identify tools that will contribute to improved clinical decision-making, prognostic evaluation and therapy in breast cancer.

Aims

- To identify genes that are specifically up- or down-regulated in breast cancer metastases in specific organs.
- To identify gene expression signatures in primary breast tumours that predict metastasis to specific organs or predict the prognosis of ductal carcinoma *in situ* (DCIS).
- To determine whether genes already associated with breast cancer invasiveness and metastasis are expressed in metastases in all or only a subset of organs.
- To demonstrate whether genes found to be specifically expressed in breast cancer metastases to given organs play a functional role in organ-specific metastasis.
- To elucidate molecular pathways that regulate breast cancer metastasis to specific organs.
- To develop improved animal models for studying organ-specific metastasis of breast cancer.
- To produce a prototype microarray chip for diagnostic/prognostic evaluation.
- To apply the findings on organ-specific metastasis in the clinical setting.

Expected results

- The results of this project will begin to explain the molecular basis for organ-specific metastasis in breast cancer.
- This project will identify regulatory pathways and cellular events that coordinate organ-specific metastasis of breast cancers. Novel targets for therapy will thereby be identified.
- This project will identify gene expression signatures in tumours associated with metastasis to particular organs. This will be an important advance in understanding the underlying genetic changes that regulate organ-specific metastasis in breast cancer.
- This project will bring together European experts working on different aspects of the molecular basis of tumour metastasis. As a result of coordinated efforts, pathways that regulate metastasis to specific organs will be determined, and genes that play a functional role in organ-specific metastasis will be identified.
- This project will generate improved animal models for the further study of breast cancer metastasis to specific organs.
- This project will identify gene expression signatures in primary breast tumours that predict patterns of metastasis. The application of these findings will assist clinical decision making and prognostic evaluation.

Potential applications

The gene expression signatures in primary tumours identified in this project that predict organ-specific metastasis and the prognosis of DCIS will have obvious potential for clinical application in diagnosis and prognostic assessment. Gene expression signatures in primary tumours associated with either organ-specific metastasis or progression of DCIS will be extensively validated retrospectively and as a prelude to introducing these gene expression signatures into clinical diagnosis and prognostic evaluation, we will perform prospective studies to demonstrate the efficacy of examining gene expression signatures in primary breast cancers for predicting the likelihood and location of metastases and the probability that DCIS will progress and metastasise after partial mastectomy. The prototype microarray chips we create based on gene expression profiles produced as part of this project will be applied in the clinical setting to investigate their diagnostic and prognostic value for breast cancer in a prospective study. This will constitute a major step towards exploitation of the results. It is also highly likely that genes are identified in this project will be candidate targets for the development of novel cancer therapies. The development of such therapies lies outside the time-frame and scope of the proposal.

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Instrument
STREP

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http://igtmv1.fzk.de/www/brecosm/

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Keywords | Identification of novel compounds | natural products | inhibition of protein-protein interactions | high-throughput screening |

CAPPELLA

Combating cancer through novel approaches to protein-protein interaction inhibitor libraries

Summary

The inhibition of protein-protein interactions (PPI) is one of the most promising approaches to the development of novel cancer therapies. This project brings together some of Europe's leading biotech SMEs and several highly recognised academic institutes. By combining fi ve distinct chemical approaches and testing them on three different targets (all from different partners) a series of innovative small-ligand tools and libraries that allow new approaches to the inhibition of PPI in cancer will be developed. The project is a unique opportunity to integrate novel *in silico,* chemical, genetic and ADME-based approaches to the design, synthesis and optimisation of libraries and compounds.

Problem

Most protein-protein interactions occur within the cell and thus can only be targeted by small molecules. Furthermore, PPI differ structurally from more classic drug targets such as enzymes and receptors, and consequently existing compounds have generally delivered disappointing results. Therefore, new approaches are needed to develop novel small molecules which inhibit PPI in cancer.

Aim

The objective of this project is to develop a series of innovative smallligand tools and libraries that allow new approaches to the inhibition of protein-protein interactions in cancer. A key theme is the utilisation of structural motifs found in natural PPI-inhibitor compounds. This is coupled with high content testing of the resultant structures on three distinct PPI targets relevant to different types of cancer, to allow compound rule-sets to be developed and improved. We want to develop small-ligand libraries focused on PPI inhibitors of relevance to cancer. Furthermore, we will develop innovative tools that allow improved library design in this area by integrating *in silico* approaches, bio-informatics, new approaches to compound synthesis and pharmacology. The project will also cover the scientifi c areas such as *in silico* prediction of drug-like properties, prediction of ADME parameters, predictive toxicology and creation of virtual libraries.

Expected results

Innovative tools for designing PPI inhibitors

- Five different PPI-inhibitor library creation tools, based on five complementary approaches:
  - *in silico*;
  - genetic chemistry;
  - advanced natural product technologies;
  - retro-synthesis of natural scaffolds;
  - ADME improvement.
- Cross-fertilisation of approaches so that each of the five approaches learns lessons from the others and incorporates relevant leanings into its approach.
- Three high-content assay systems for three important PPI cancer targets (p53-Mdm2, Beta catenin-TCF4, BRCA2-RAD51).
- Design rules for PPI inhibitor compound libraries (mass, diversity composition, lipophilicity, compound class etc.) generated from 15 complementary data sets.

Novel small-ligand libraries and pre-clinical candidates

- Several 'PPI inhibitor' compound libraries.
- Different candidate compound families from within these libraries that can subsequently be taken forward into pre-clinical testing by the SME partners.

Libraries containing extracts of biological material offer great chemical diversity.

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Instrument
STREP – SME

Project website
www.cappellabio.eu

Keywords | Systems biology | modelling | simulation | functional genomics |

COMBIO

An Integrative Approach to Cellular Signalling and Control Processes – Bringing Computational Biology to the Bench

Summary

The project combines a unique group of experimentalists, bioinformaticians and simulation groups in order to gain detailed understanding of key processes: the P53-MDM2 regulatory network and the self-organisation process whereby chromatin controls microtubule nucleation and organisation. A major objective will be to benchmark the ability of current modelling and simulation methods to generate useful hypotheses for experimentalists and to provide new insights into biological processes of realistic complexity.

Problem

It is increasingly being recognised that the progress of modern day biology will require understanding and harnessing the network of interactions between genes and proteins, and the functional systems that they generate. Given the complexity of even the most primitive living organism, and our still very limited knowledge, it is unreasonable to expect that we might, in the near or even medium term, reach such understanding at the level of an entire cell. However, significant progress towards a system-level understanding should be achievable by applying an integrated approach to the analysis of a set of well-defined and biologically important cellular processes.

Aim

It is not our goal here to come out with a new software package, or to simulate a whole cell. Rather our project aims to bring computer models and simulations to the experimental community. To do so we will focus on two systems involving different aspects of biological systems: networks and self-organisation and we will apply different simulation approximations to both of them. This will enable us to identify both the modelling and the simulation strategies that are better suited for a particular experimental problem.

Expected results

The expected result will be a set of guidelines specifying which, and how, simulation methods should be used, given the problem at hand. These guidelines will also indicate how best simulations and experimental procedures might be combined to answer key questions about biological function.

Potential applications

The generation of the guidelines described above should make a fundamental contribution to the area of functional genomics, and provide ways for elucidating the mechanisms of action of pharmacological compounds.

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LSHG-CT-2004-503568

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€ 1 998 000

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42 months

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Instrument
STREP

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Keywords | Oncology | anticancer therapy | clinical pharmacology | uncommon cancer | sarcomas | GIST | children | adults |

CONTICANET

Connective Tissue Cancers' Network to integrate the European Experience in Adults and Children

Summary

Connective tissue cancers, and more specifically sarcomas, GIST, aggressive fibromatosis and hamartomas, are uncommon cancers with an incidence below 2/100 000 per year in the EU affecting children, young adults and adults. At a national level, the limited number of cases (about 7/10 000 in Europe each year) does not allow Europe to have a critical mass of researchers and the supporting environment to progress in the disease understanding and management and to have access to new drugs and treatments. Europe, however, has proven with research made on GIST, through the EORTC-STBSG group, that gathering workforces can achieve significant progress. CONTICANET will create the critical mass of key stakeholders to overcome the current difficulties in terms of lack of data and data fragmentation, mobility of researchers, heterogeneity of methodologies and legislations.

CONTICANET will:

- start by providing the required environment for developing joint research activities through the development of standard operating procedures (SOP), distributed databases, tissue banks and harmonisation of ongoing and previous research projects, to promote complementarity and perform parallel research programmes according to similar SOPs;
- provide the infrastructure to test several drug candidates and perform European wide exploratory clinical trials while implementing a federated research policy;
- further lead to an integrated sustainable structure – a European research foundation – able to support integrated research actions and make new treatments available.

Involving 20 partners – major comprehensive cancer centres, academia and private companies – over a period of five years, CONTICANET will gather the critical mass of resources and knowledge in the understanding, diagnosis and clinical management of connective tissue cancers, at the same time opening new therapeutic options.

CONTICANET will spread excellence in several directions: enlarging the network with other academic and private organisations; developing working sessions with EMEA, health authorities and insurances in order to optimise the availability of new therapeutic options; supporting and collaborating with patients through advocacy groups and cancer leagues.

Problem

Scientific challenges

- Connective tissue tumours: a collection of rare tumours.
- Molecular characterisation is routine for few tumours, in progress for other tumours but unknown for most tumours.
- There is a need for harmonisation of research activities in the following fields:
  - molecular characterisation of these tumours,
  - functional genomics.
- Pharmacology: target characterisation and validation.
- Promotion of clinical and translational research.
- Improvement of medical practices.
- Education of the physicians for CPGs.
- Epidemiology and medical economics.

Medical challenges

- Demonstrated 'proof of concept' for several connective tissue subtypes.
- Targeted oncogene treatments are active treatments.
- Harmonisation of research activities, medical practices and education in a context where:
  - patients are not always treated in specialised centres;
  - most patients are not treated according to CPGs;
  - structured clinical research and TR in large centres and network.
- Medical practices do not follow clinical practice guidelines for more than 60% of patients in most western countries so there is a need for education of physician and patients.

Economical challenges

Health:

Inappropriate management results in increased costs.
Survival and functional disabilities in adults and children.

Identification of novel targets and treatment:

Generate intellectual propriety.
Commercialisation of new agents.

Transfer towards industrial partners:

Perform rapid proof of concept clinical trials.
Generate synergy between European academia and industry.

Political challenges

Strengthen and harmonise European research in these rare tumours:

Establish the network as the worldwide leading force for research in these rare tumours.

Promote academic and industrial collaborations:

Generate a network with integrated joint research programmes.
Include new partners from academia, industry and patients advocacy groups.

Ensure the long term viability of the network.

Aim and expected results

CONTICANET aims at setting up a Network of Excellence as a vehicle to create the critical mass of researchers, clinicians and industrialists able to:

- improve the understanding of carcinogenesis and tumour progression of connective tissue cancers in adults and children and specifically of sarcomas, GIST, aggressive fibromatosis and hamartomas;
- develop new diagnostic tools, prevention strategies and treatments for these connective tissue cancers in adults and children.

The main goals of CONTICANET are to:

- create the critical mass of key stakeholders from translational, pharmacological and clinical research to make a real breakthrough in connective tissue cancer diagnosis and management, both for adults and children;
- capitalise on pre-existing collaborations to set up, implement and update a joint research programme and then a European-wide organisation covering pre-clinical and clinical research on connective tissue cancers with a patient to patient approach;
- make available to all participants a strong network of facilities accelerating research output.

From this integration, CONTICANET will provide a basis for the development of new treatments and, from an industrial point of view, to:

- establish synergisms between data and models acquired by academics and drug development from the pharmaceutical industry to improve therapeutic options for both adults and children;
- validate some of those options with competent authorities as a model for orphan disease.

CONTICANET will spread the excellence achieved in the network to:

- improve training of health professionals in charge of diagnosis and multidisciplinary primary care of the European patients through the production of guidelines and reference for medical practice. In particular, strong relationships already exist – and will be reinforced – between the consortium and:
  - the European Society of Medical Oncology – ESMO (all);
  - the EORTC (ERASM, UCBL, IGR, INT, ICR, MAUNIHEI);
  - the European Society for Surgical Oncology – ESSO (INT, UCBL, IGR, ICR, MAUNIHEI);
  - the European Society for Therapeutic Radiation Oncology – ESTRO (UCBL, SLS, IGR, UNIPD, ICR);
  - the European Musculo Skeletal Oncology Society – EMSOS (INT, IGR, SLS);
  - the European paediatric Soft tissue Sarcoma Group – EpSSG (UNIPD, ICR, IGR, CURIE, BERGONIE);
  - but also with international societies: the world wide Connective Tissue Oncology Society – CTOS (UCBL, IGR, ICR, ERASM, INT, MAUNIHEI);
  - and European organisations such as orphanet Europe, research directorate by contributing to the European effort on rare diseases (www.cordis.lu/lifescihealth/major/rare-diseases.htm).
- inform, get feedback from, collaborate with and support patients advocacy groups (SOS-Desmoides, Jeunes Solidarité Cancer, Life Raft);
- interact with EMEA, health authorities, social security and insurances;
- involve other pharmaceutical, biotech and academic centres in the EU to enlarge the capacity of the network;
- reinforce collaborations outside Europe, in particular with Canada (McGill University), Russia (NCI Moscow), Israel (Weizman Inst.), USA (MSKCC) and Australia (Peter MacCallum Cancer Institute) Finally CONTICANET will generate three different types of results:
  - an organisation gathering key stakeholders in connective tissue cancer research and able to perform significant progress in the disease understanding and management through jointly performed studies in the fields of epidemiology, molecular biology research, clinical research, drug development. This organisation will take the form of an international non-profit association gathering all network participants. This association will then in a second step evolves towards a research foundation open to new members and to sponsors. By involving pharmaceutical companies and with the objective of extending the approach to other uncommon cancers, such a foundation will be self-sustained through the contributions of its members and the support to be obtained form the industry through the development of orphan disease models;
  - the delineation of methods, tools and activities which will be developed within the network and supporting the integration of the research activities of the participants and which will be shared among participants and ultimately beyond the network to strengthen research in this field:
    - distributed standardised repository of tissues, data, information supporting research activities;
    - standardised Operating Procedures (SOP) at European level;
    - common pool of facilities: instruments, platforms, drugs, diagnostic tools, etc.;
    - collaborative platform for data transfer and validation and collaborative work;
    - network for pharmacodynamics based clinical trials;
    - standardised validated screening tools (*ex vivo* & *in vivo*);
    - pharmacovigilance network;

- public health research coupled with education aiming to understand the determinants of medical practice in order to propose innovative education strategies to improve patient management and follow up. Knowledge gained in this field will be disseminated within the network and beyond by the key opinion leaders present in the network in their respective countries.

Once these goals are achieved for sarcomas, GIST, aggressive fibromatosis and hamartomas, the consortium will choose other types of uncommon connective tissue tumours (primary CNS tumours, mesotheliomas) and ultimately aim at contributing to integrated research in the field of uncommon epithelial cancers (neuroendocrine cancers, adenoid cystic carcinomas). Thus the CONTICANET network is expected to develop on the long term a stable structured European research organisation on uncommon cancers and could possibly serve as a model for other rare diseases.

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LSHC CT-2005-018806

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60 months

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01/02/2006

Instrument
NoE

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Keywords | Functional genomics | systems biology | regulatory networks | dynamical modelling |

DIAMONDS

Dedicated Integration and Modelling of Novel Data and Prior Knowledge to Enable Systems Biology

Summary

We will demonstrate the power of a systems biology approach to study the regulatory network structure of the most fundamental biological process in eukaryotes: the cell cycle. An integrative approach will be applied to build a basic model of the cell cycle in four different species including S. cerevisiae (budding yeast), S. pombe (fission yeast), A. thaliana (weed, model plant) and human cells. To do this, a consortium has been assembled of leaders in the fields of cell cycle biology, functional genomic technologies, database design and development, data analysis and integration technology, as well as modelling and simulation approaches. The project combines a number of complementary data sets toward an advanced mining and modelling environment, designed to assist the biologist in building and amending hypotheses, and to help the investigator when designing new experiments to challenge these hypotheses. By doing these simultaneously in widely different organisms, we will ensure that the tools are generally applicable across species. By bringing together biologists, bioinformaticians, biomathematicians and (commercial) software developers in the design phase, we will ensure that a user-friendly, intuitive data analysis environment is created. The main data streams generated de novo within the project concern transcript profiling and proteomics data (Y2H and TAP). These data will be complemented with information extracted through comparative genomics, and prior knowledge coming from literature mining (text mining tools). The project will bring together a number of existing technologies to build a knowledge warehouse in a relational database designed to contain cell cycle regulatory network information, accessible through an intuitive user platform (GUI) with embedded modelling tools. This platform will enable both top-down and bottom-up hypothesis-driven research, and will serve as a basis to develop more rigorous dynamical models for cell cycle variants.

Problem

Cell division is regulated by highly conserved genetic networks. Occasionally the cell division machinery becomes unstable, resulting in an uncontrolled proliferation of cells. In humans, the uncontrolled division and growth of cells can lead to cancer. Cell division is also at the core of biomass production and agricultural yield. A better understanding of the processes that regulate cell division is therefore of prime importance for human health, welfare and sustainable development. The approach taken by DIAMONDS constitutes a pioneering step toward the application of a systems biology approach for genetic network analysis, and as such will contribute to the maturation of systems biology into a general approach, complementary to the traditional gene-by-gene approach. With the rapid increase in genome sequences, published literature and databases on proteomic and transcriptomic data, it is obvious that integrative analysis, bringing together various complementary data types for the identification of network motifs, should be tested on well-defined biological models to assess the potential of a systems biology approach.

Aim

The overarching objective of this multidisciplinary project is to demonstrate the power of a systems biology approach to study fundamental biological processes. We focus on eukaryotic cell cycle regulation, and will develop and implement a computational model that will function as a hypothesis-generating engine in a systems biology 'wet-lab' environment. The work will be done in a number of wet-labs and dry labs, on yeast, plant and human cells, to make sure that the approach is validated across widely different organisms. The main target of the project consists of two parts:

- a cell cycle knowledge base and an integrated platform of data mining, modelling and simulation tools that will allow the integrated analysis of that data in a systems biology approach;
- the development of a basic model, the use of this model to design new experiments, the production and analysis of novel data, and the integration of these into a refined model.

The knowledge base and tools will be made available and introduced to the European research community.

The principle method to reach this target is to harvest and/or produce a large body of cell cycle-related biological knowledge. This will function as the central resource for the modelling and simulation environment that will be developed. As mentioned above, the knowledge warehouse will constitute one of the major deliverables of the project, enabling future hypothesis-driven research. The project will showcase the fact that a systems biology approach towards analysis of a fundamental biological process can in fact become mature today, and hinges on an integrated data analysis pipeline, extended with modelling and simulation tools. The essential elements of such a pipeline will be: functional genomics data production (transcriptome and proteome); literature mining; comparative analysis of genes and networks; a visualisation, modelling and simulation environment, and a web service-based data integration layer.

Project number
LSHG-CT-2004-512143

EC contribution
€ 2 500 000

Duration
36 months

Starting date
01/01/2005

Instrument
STREP

Project website
www.SBcellcycle.org

Expected results

We will construct an integrated toolbox for the analysis of functional genomics data, and the modelling of cell cycle information for simulation purposes. We will also deliver a knowledge base (GIN-db) containing detailed information about core cell cycle genes.

Potential applications

The concerted efforts in DIAMONDS will allow extensive data integration and modelling, and will deliver new insights in cell cycle regulation and the mechanisms that prevent the uncontrolled proliferation of cells, opening the way to novel anti-tumour drugs and strategies. The potential for applications of life sciences and biotechnology promises to be a growing source of wealth creation in the future, leading to the creation of jobs, particularly in the areas of highly skilled labour, and new opportunities for investment in further research.

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Keywords | DNA damage | genome (in)stability | cancer pre-disposition | genomics | proteomics | mouse models |

DNA Repair

DNA Damage Response and Repair Mechanisms

Summary

This project focuses on unravelling the mechanisms of DNA damage response and repair, an area with a major impact on human health, notably cancer, immunodeficiency, other ageing related-diseases and inborn disorders. The project brings together leading groups with multi-disciplinary and complementary expertise to cover all pathways impinging upon genome stability, ranging from molecules to mouse models and human disease.

The main objective is to obtain an integrated perception of the individual mechanisms, their complex interplay and biological impact, using approaches ranging from structural biology to systems biology. The translation of the results that we obtain is expected to contribute to an improved quality of life through:

- possible identification of genetic markers for assessment of susceptibility to occupational hazards and disease;
- discovery of promising targets for therapy;
- improved diagnostic and prognostic procedures for genetic disorders;
- early diagnosis and prevention of cancer and other ageing-related diseases. We have also included a strong training component in the project to invest in young talented students for the future.

To understand the function and impact of DNA damage response and repair systems in living organisms better, we will take full advantage of our existing unique and extensive collection of models (mutant yeast cells and mice), and engineer and analyse new mutants impaired in genome stability. The rapid growth in genomic and proteomic technologies will be exploited to identify novel genes involved in genome surveillance. We will use bioinformatics and high-throughput systems for analysis of gene expression, and proteomics to identify putative functions of such genes and their proteins, as well as similar global genome analytical tools to identify interactions with, and effects on, other cellular processes. The 'drugability' of potential targets to improve anti-cancer therapy will be tested in collaboration with SMEs. Through existing contacts with clinicians we will continue to analyse patients with previously identified defects in DNA damage response and repair mechanisms, and use our clinical contacts to screen for new disorders.

Background

The pleiotropic effects, inherent to the time-dependent erosion of the genome and the complexity of the cellular responses to DNA damage, necessitate a comprehensive, multi-disciplinary approach, which ranges from molecule to patient. At the level of structural biology and biochemistry, individual components and pathways will be analysed to identify new components and clarify reaction mechanisms. The interplay between pathways and cross talk with other cellular processes will be explored using both biochemical and cellular assays.

Aim

To get to grips with the vast problem of DNA damage, an integrated, multidisciplinary approach is imperative. The level of understanding of many individual pathways has strongly increased through worldwide research in which European teams have played a prominent role. The main questions and challenges ahead are:

- moving from understanding distinct pathways towards the complex interplay between the various genome stability systems putting these pathways in an integrated cellular context, perfectly fitting into the concept of integrated projects;
- insight into the clinical impact of the systems individually and collectively from the cellular level to that of intact organisms, and extending to the human population;
- translation of this knowledge into practical applications in terms of improved diagnosis, effective therapy and prevention or postponement of diseases associated with the functional decline of the genome.

Expected results

- A detailed understanding of the biochemical mechanism of DNA repair and checkpoint pathways.
- Insight into the cellular functioning and consequences of defects in one of the genome surveillance pathways.
- Identification of new components of DNA damage response pathways.
- Extension of knowledge from model organisms to humans. This will be accomplished by the investigation of patients and cells from patients suffering from genome instability, cancer predisposition and premature ageing syndromes, and also by an extensive comparison of mouse mutants with human diseases involving genome instability, cancer predisposition and premature ageing.

Project number
LSHG-CT-2005-512113

EC contribution
€ 11 500 000

Duration
48 months

Starting date
01/05/2005

Instrument
IP

Project website
erasmusmc.nl/dna-repair/index.php

Potential applications

Our DNA is under constant attack from physical and chemical agents that compromise its integrity and form a potential danger for genomic stability, which may result in cancer and other health problems. A large number of chemical compounds in our food have a potentially harmful influence on our genetic make-up, especially under conditions in which the DNA repair capacity is sub-optimal. The proposed research will be of prime importance to assess potential risks posed by environmental hazards (such as food components or environmental pollutants).

A better understanding of the genome-wide responses to genotoxins in relation to the DNA repair status of an organism will enable evaluation of possible risks to consumer health and thereby help eliminate sources of danger to human health. Our genomics and proteomics approaches have applications for the assessment of the health risks of such compounds for specific subgroups carrying subtle mutations in DNA repair genes and for the ageing population. Thus, the advances in insight generated by the integrated project have the potential to be of major importance for rational risk assessments pertaining to drug development, environmental pollutants and occupational hazards.

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Keywords | Cancer | biomarker | *in situ* analysis | technology development | proximity ligation | padlock probing |

ENLIGHT

New molecular methods and image analysis tools for analysis of cancer biomarkers *in situ*

Summary

The ENLIGHT project has the purpose to develop analytical procedures with the sensitivity and specificity required to study individual nucleic acid and protein molecules, and also interacting molecules, in their normal context in cells and tissues (*in situ*) and in tissue lysate microarrays. A spectrum of reagents will be developed for the analysis of specific markers of particular interest in oncology. Furthermore, we will establish software and algorithms for automatic user-independent *in situ* image analysis of single molecule-events. These methods and algorithms will be applied to evaluate candidate biomarkers of special relevance for tumour biology and cancer pathology.

Problem

In situ analysis of cells and tissues has been an essential part of pathological research and diagnosis primarily within cancer for many years, and a number of specific biomarkers of predictive and prognostic value for various cancers have been identified. *In situ* analysis of nucleic acid sequences is dominated by *in situ* hybridization, while *in situ* analysis of proteins is dominated by immunohistochemistry where sections of tissues are tested for the presence of proteins by specific antibodies. Due to limitations in these technologies there is a significant need in the scientific community for new efficient techniques and procedures for more advanced analyses. A major challenge is to develop improved means for more detailed studies of biomolecules *in situ,* in order to determine their abundance, sub-cellular localization, and secondary modifications, as well as how they interact with other molecules and participate in signalling and control of cellular function.

Aims

The first aim is to develop new molecular methods and assays for the analysis of individual DNA and protein molecules *in situ.* The project is based on two fundamental technological inventions, padlock probing and proximity ligation. These are the first technologies to offer the sensitivity and specificity required for studies of single bio-molecules *in situ.* The padlock probe technology is used to interrogate nucleic acids and to distinguish closely similar sequence variants, while the proximity ligation assay (PLA) is applied to analyze individual proteins, interactions between proteins, and post-translational protein modifications.

As a second aim we will develop automated image analysis procedures to complement the molecular methods. The objective is to achieve quantitative information about what molecules or molecule complexes are present in the sample and their tissue or sub-cellular localization (i.e. in which cellular substructures).

The third aim is to use the new methods and image analysis procedures to clarify the role of molecular biomarkers in tumourigenesis, primarily concerning the AP-1 and HER protein families and for mitochondrial DNA. The methods will also be tested in a high-throughput microarray analysis system. The cancer biomarker will primarily be investigated in a research setting, but we will also explore the utility of the markers for diagnostic analyses.

Expected results

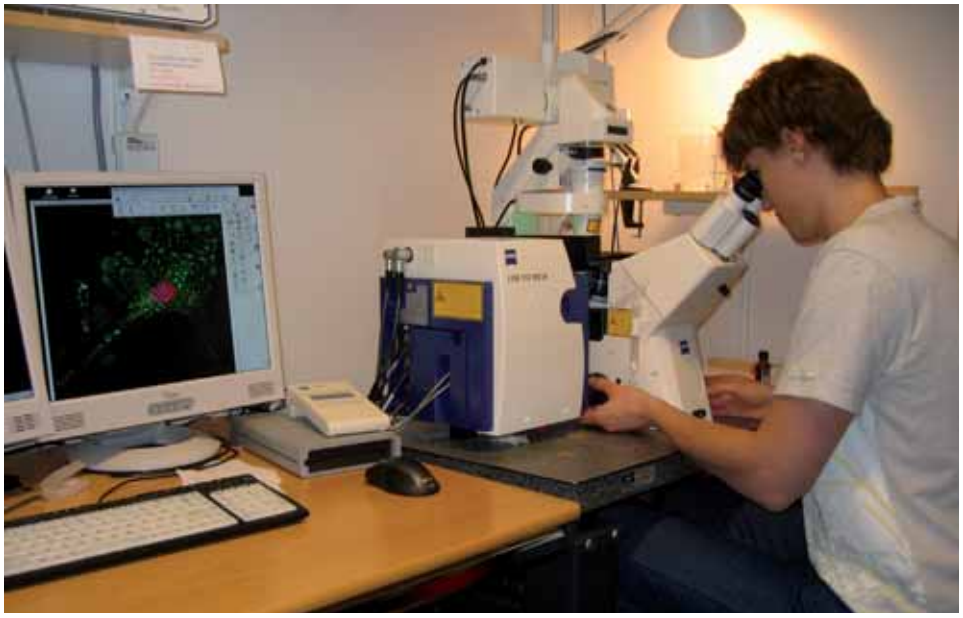
This project is expected to provide new means to study biomarkers for oncogenesis, and to generate novel insights in cancer biology. We expect that the *in situ* techniques developed in this project, and the scientific knowledge created, in the longer run will lead to improved disease prevention, more rapid and accurate cancer diagnosis, and better treatment opportunities.

New analytical means will be developed to analyse cancer biomarkers *in situ.* Relative to state-of-the-art procedures, these methods are expected to provide significantly improved *in situ* analyses in terms of specificity, sensitivity (single molecule detection), possibility to study biomarker localisation, analysis of protein interactions and protein modifications, and an opportunity for simultaneous analysis of multiple markers (multiplex analysis). Automated image analysis procedures will be developed, i.e. software-based classification of molecules and their localisation in tissues or cells. The software will provide a rapid way to analyse many samples as well as user-independent, unbiased data classification.

The results from this project are furthermore expected to provide new commercial opportunities for products addressing significant market needs, thereby allowing the participating European SMEs to build sustainable businesses at the forefront of biotechnology.

Potential applications

Cancer biology and diagnosis.



Microscopic examination of tissue sections.

Project number
LSHB-CT-2006-037545

EC contribution
€ 2 978 810

Duration
36 months

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01/08/2006

Instrument
STREP

Project website
www.olink.com/enlight.html

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Keywords | Epithelial stem cell | keratinocyte differentiation | p63 and family members | EEC-related syndromes |

EPISTEM

Role of p63 and Related Pathways in Epithelial Stem Cell Proliferation and Differentiation and in Rare EEC-Related Syndromes

Summary

The focus of EPISTEM is to generate new knowledge and translate it into applications that enhance human health. To this end both fundamental and applied research will be involved. EPISTEM integrates multidisciplinary and coordinated efforts to understand the molecular basis of factors involved in epidermal stem cell generation, maintenance and differentiation and skin disease. Moreover, the core molecule that will be studied in this Integrated Project is p63 (and related pathways), a molecule genetically proven to be involved in the development of rare skin diseases. Collectively, the prevalence of ectodermal dysplasia syndromes (EDS) is estimated at seven cases in 10 000 births. Currently there is no cure for these patients. By creating the EPISTEM consortium, we want to address, from different angles (i.e. via genetics, gene profiling, molecular and cellular biology, structural biology, drug design and bioinformatics), the molecular pathways involved in epidermal dysplasia syndromes making use of different technologies (mutation analysis, micro-array, ChiP, transgenes, proteomics, *in vitro* skin cultures, crystallography, etc.). Our consortium brings together leading European clinicians, geneticists, molecular and cellular biologists, structural biologists, a drug designer and bioinformatics specialists in the field of p63 (and related molecules) research.

Problem

The core molecule that will be studied by the EPISTEM consortium is p63 (and related pathways), a molecule genetically proven to be involved in the development of rare skin diseases such as EEC syndrome (Ectrodactyly-ectodermal dysplasia – clefting), Hay-Wells (AEC) syndrome, Limb-mammary syndrome, ADULT syndrome, Rapp-Hodgkin syndrome and non-syndromic split hand-split foot malformation. Currently there is no cure for these patients.

Aim

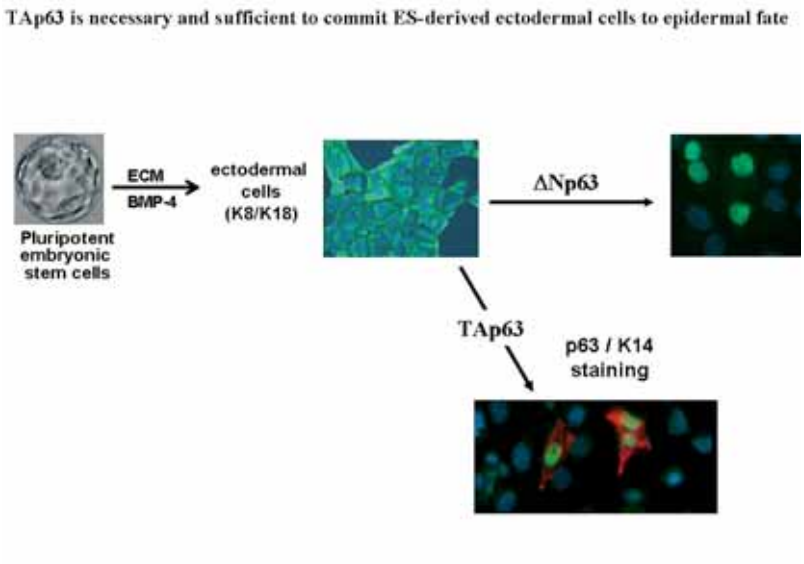
- Collecting and culturing of keratinocytes from EDS patients with p63 mutations and extensive analysis of phenotype-genotype correlation. These keratinocytes will be used to uncover the role of p63 proteins and pathways in normal and abnormal skin development.
- Building relevant *in vitro* and *in vivo* skin disease models for studying the role of p63 in EDS disease and the genetic assessment of novel pathways discovered during this project. These models will also be used for drug assessment.
- Provide insight into the regulation and involvement of p63 and related pathways in skin differentiation, the maintenance of the proliferative capacity of epithelial stem cells and the transition of ectodermal cells to epidermal stem cells.
- Screening for, and design of, novel therapeutic drugs, based on three-dimensional p63 models, that will refold/reactivate or inhibit p63 mutants and induce biological responses in relevant disease models.

Expected results

First of all, the EPISTEM consortium will generate a thorough insight into the molecular biology of a rare disease such as EDS, for which no cure is currently available. Secondly, characterising and understanding how epidermal stem cell maintenance is regulated by p63 could be beneficial for the treatment of burn victims since these stem cells could be used for tissue regeneration. So, in the long run, the EPISTEM research proposal may have a far broader impact on clinical practice and the biomedical industry than is currently estimated. Thirdly, this integrated project will generate knowledge and technology that is not only applicable to p63 itself, but also to its family members p53 and p73; p53 is an important target that is mutated in most cancers and p73 is an important molecule for neurogenesis. Finally, from a technological point of view, the EPISTEM proposal will invest in the development of chIP (chromatin immunoprecipitation) on chip technology.

Potential applications

Drug-development for the cure of skin diseases, cancer, etc. and a wound-healing treatment.



Pluripotent embryonic stem cells are cultivated on glass coverslips coated with fibroblast-secreted matrix proteins (and probably trapped growth factors and cytokines). Undifferentiated ES cells are induced to differentiate by removal of LIF (Leukaemia Inhibitory Factor) and the addition of BMP-4 (Bone Morphogenetic Protein-4). These cells were transfected with transduction-competent (TAp63) and transduction-incompetent (Np63) expression vectors. The presence of ES-derived keratinocytes is scored using an antibody against the cytokeratin-14 intermediate filament. These experiments show that TAp63 is capable of inducing keratinocyte differentiation starting from a stem cell population. Which cellular programmes are involved in this process remains to be determined.

Project number
LSHB-CT-2005-019067

EC contribution
€ 8 130 000

Duration
48 months

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Instrument
IP

Project website
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Keywords | Epigenetic | apoptosis | differentiation |

EPITRON

Epigenetic treatment of neoplastic disease

Summary

Chromatin is epigenetically modified to regulate gene expression. Upstream signals induce complex patterns of enzyme-catalysed modifi cations of DNA and histones, key protein components of chromatin. These epigenetic modifi cations create docking sites and form a code that specifi es transient or permanent (and heritable) patterns of genome function. In addition, epigenetic enzymes modify the activity of major transcription factors. Emerging evidence causally links altered epigenetic functions to oncogenesis, and suggests that chromatin regulators and upstream pathways are critical targets for developing novel anti-cancer drugs (epi-drugs). EPITRON will defi ne and validate the concept of 'epigenetic cancer treatment' from the molecular mechanism(s) to animal models reproducing human cancers. EPITRON will establish a programme from drug target exploration and drug development to preclinical validation *in vitro, ex vivo* and *in vivo.* Epi-drugs are amongst the most important novel drugs that have been generated to treat cancer, as can be concluded already from the existing results obtained with HDACi's, some of which performed very well in phase I and phase II clinical trials. EPITRON is unique in its efforts to strengthen European biomedical and pharmaceutical competitiveness. It fosters an exchange of biomedical knowledge, technology and materials among European laboratories, provides opportunities for education and training – and creates jobs.

Problem

Elucidating the 'signatures' of cancer cells is one of the four so-called 'extraordinary opportunities for immediate investment' defi ned by the National Cancer Institute of the United States of America. These four priorities (defi ning the signatures of cancer cells, cancer genetics, preclinical models of cancer and imaging technologies) were selected as top priorities to receive privileged attention and funding. Thus the EPITRON project aims to contribute at multiple levels to the definition of epigenetic signatures of cancer.

Aim

The overall goal of EPITRON is to validate and extend the concept of 'epigenetic therapy' of cancer. For this a pipeline will be established, which extends from the analysis of epigenetic (de)regulation in cancer to the study and generation of epi-drugs in a multiplicity of *in vitro, ex vivo* and *in vivo* mouse models. We will develop and use mouse models that accurately reproduce the human disease. The particular goals of EPITRON are:

- to study the epigenetics of cancer cells (with a focus on leukaemia, breast and colon cancer), and defi ne the mechanisms of (cancer selective) action of epi-drugs;
- to establish the basis of the cancer-selectivity of TRAIL/TRAIL receptor action;
- to identify novel epi-drug targets;
- to synthesise novel epi-drugs with increased effi cacy/tumour selectivity;
- to validate epi-drug target therapy of cancer *in vitro* (primary normal and tumour cells), *ex vivo* (leukaemic blasts vs. normal progenitors) and *in vivo* (mouse models which accurately reproduce human cancer; the focus will be on APL/AML but also solid cancer models will be used or established).

Taken together, EPITRON will not only provide information about epigenetic modifi cation imposed upon cancer cells, validate existing and generate novel epi-drugs, but most importantly engage upon a major challenge of cancer therapy by devising treatments that kill cancer, but not normal cells.

Expected results

To validate and extend the concept of 'epigenetic cancer therapy', EPITRON will follow six axes of research, focused on preclinical models.

- Mechanisms of anti-leukaemic action of epigenetic drugs. We will defi ne the anti-leukaemogenic potential and the corresponding mechanistic basis of existing epigenetic drugs used alone or in combination, and in combination with other signalling drugs, such as nuclear receptor ligands. The impact of chromatin modification (DNA, histones) that correlates with tumourigenesis and underlying recognition principles will be studied.
- Oncofusion genetic and epigenetic programmes. We will use cell lines, patients' blasts and mouse models to understand the altered gene programming due to the oncogenic fusion protein(s).

- Decryption of the leukaemia cell-selective apoptogenic action of TRAIL. Based on the original fi nding of members of this consortium that several anti-leukaemogenic treatments activates the TRAIL death pathway, and the observation that TRAIL signalling induces apoptosis in tumour, but not normal cells, the molecular mechanism(s) underlying this fascinating potential will be defi ned in suitable cellular models using a plethora of genomic technologies.
- Therapeutic potential and toxicities of TRAIL in animal models. Based on regulable TRAIL expression systems, EPITRON will establish mouse models to assess the spectrum of anti-cancer activities and possible toxicities of TRAIL *in vivo* using both ubiquitous and tissueselective expression paradigms. At the same time 'reporter mice' will be created, which will allow monitoring activation of the TRAIL signalling pathway by (epi-)drugs.
- Generation and validation of novel epigenetic drugs. Crystal structures and innovative chemistry will be used to generate compounds that (selectively) modulate the activity of epigenetic enzymes/machineries.
- Models for epigenetic therapy of solid cancers. Among the several tumour mouse models used by EPITRON, studies will be performed to assess effi cacy and mechanisms of HDACi and novel EPITRONgenerated epi-drug actions in breast cancer models. In these studies, primary cell cultures derived from the above mouse models (and their normal counterparts) will also be used. Moreover, EPITRON will establish as a novel tool matched pairs of primary normal and cancer cells from the same patients to assess (epi-)drug action, especially tumourselective activities. As an example of a gender cancer, primary patient-matched cultures of normal and breast cancer epithelial cells will be studied.

Potential applications

In their entirety, the studies performed in AML, breast, skin and colon cancer preclinical models will provide a framework for a detailed molecular defi nition of 'epigenetic therapy', which will pave the way to more focused and appropriate protocols for future clinical trials.

Project number
LSHC-CT-2004-518417

EC contribution
€ 10 904 474

Duration
60 months

Starting date
01/11/2005

Instrument
IP

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Keywords | Bone tumour | chondrosarcoma | osteosarcoma | giant cell tumour of bone | Ewing's sarcoma | osteochondroma | Paget disease of bone | chondrogenesis | osteogenesis |

EuroBoNeT

European Network to Promote Research into Uncommon Cancers in Adults and Children: Pathology, Biology and Genetics of Bone Tumours

Summary

Primary bone tumours are rare, accounting for ~0.2% of the cancer burden. Children and young adolescents are frequently affected. The aggressiveness of these tumours has a major impact on morbidity and mortality. Though progress has been made in pathological and genetic typing, the aetiology is largely unknown. Advances in therapeutic approaches have increased survival rates, but a signifi cant numbers of patients (~40%) still die. Within the EuroBoNeT, staff exchange, share of material and technologies, as well as the organisation of training courses, will be used to increase and disseminate knowledge of primary bone tumours. Exchange of material, standard operating protocols, and the use of technology platforms will enable us to obtain statistically signifi cant datasets. A joint programme will contribute in obtaining molecular portraits of tumours, separated into four research lines: RL1: cartilaginous tumours; RL2: osteogenic tumours and related sarcomas; RL3: osteoclastogenesis and giant cell tumours of bone; and RL4: the Ewing family of tumours. The tumours will be examined by genome-wide expression, genomic aberration studies, and specifi c hypothesis-driven approaches (RNA/protein expression and mutation analysis). *In vitro* studies will be used to obtain knowledge of normal growth and differentiation, and this may help to identify markers for malignant transformation and/or progression, as well as identifi cation of therapeutic targets. Dissemination of knowledge will be achieved by training courses on bone and soft tissue pathology. This is essential since patients do not normally present themselves at centres, and it is important to share such knowledge.

Problem

Bone sarcomas are rare and represent a group of cancers that occur predominantly in children and young adults. Intrinsic to their aggressive behaviour, these tumours are lethal in about 40% of patients despite modern multimodality therapy. Although substantial progress has been made over the last 10 years in understanding these tumours at the biological, pathologic and genetic level, this has not been translated into more effective therapies so far.

The 2002 WHO classification recognises 32 different entities of bone tumours. Achieving significant numbers to study the different types of bone tumours, which are already rare as a group, is difficult. The research into these tumours is often performed in relatively small research groups, which are inherently hampered by the lack of availability of substantial numbers of cases, as well as lacking a critical technical and/or multidisciplinary mass. Interestingly, despite their rareness, these tumours provide excellent examples for unravelling oncogenic mechanisms.
The main problems are:

- collecting enough tumours to obtain reliable significant statistical results, also when comparing subtypes based on locations, grade, etc.;
- since osteogenic and Ewing's family of tumours are considered orphan diseases, pharmaceutical companies will not invest in developing new drugs;
- chemotherapeutic treatment can be toxic for the patient or not effective, and there are no tools that predict which patients are hypersensitive or which tumours are refractory;
- cartilaginous tumours are resistant to treatment other than surgery. This can be mutilating and it is not always feasible to remove the whole tumour (for instance in the pelvic area);
- a small percentage of benign cartilaginous tumours develop into malignant chondrosarcomas, but there are no clues to recognising the ones that will deteriorate;
- the biological behaviour of giant cell tumours is variable and cannot be predicted so far. In a small proportion of tumours, synchronous or metachronous metastases develop;
- the biology of normal chondrogenesis and osteogenesis is complex. A better under-standing of the pathways involved could provide clues to the biology of bone tumours.

Aim

The above-mentioned major problems will be handled by EuroBoNeT in the following ways:

- to overcome the spread of samples and lack of critical technical and/or multidisciplinary mass in some of the institutes, the main objective will be to reach integration through sharing of samples, sharing of technologies and incorporating all information gathered by the different partners. This will be done through staff exchange, core facilities, a virtual BioBank and combining each others' experimental results;
- the EuroBoNeT will characterise the tumours in the different research lines by proteomics, genome-wide expression analysis, and genomic array. This will provide a large data set, which can be compared within and between the different tumour (sub)types. These data will be used for:
  - identification of loci involved in conferring hypersensitivity or chemotherapy resistance;

Project number
LSHC-CT-2006-018814

EC contribution
€ 13 218 960

Duration
60 months

Starting date
01/02/2006

Instrument
NoE

Project website
www.eurobonet.eu

- identification of molecular targets for therapy;
- identification of markers involved in malignant transformation;
- identification of genes/pathways involved in disease progression.

- by studying the molecular mechanisms involved in osteoclastogenesis and chondrogenesis (using *in vitro* models), EuroBoNeT aims to identify new mechanisms that could also play a role in bone tumourigenesis, and provide clues for the identification of new diagnostic and/or prognostic markers.

Expected results

The establishment of a lasting network in which samples will be exchanged and results combined and discussed, and that will be able to:

- provide uniform guidelines for bone tumour pathology;
- play a role in the development of:
  - new diagnostic markers,
  - new prognostic markers,
  - markers to predict the effect of chemotherapeutics,
  - new drug treatment.

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Keywords | Cancer | stem cells | leukaemia | breast cancer |

EuroCSC

Targeting Cancer Stem Cells for Therapy

Summary

Cancer remains one of the leading causes of death in the western world and, while chemotherapy has provided a major improvement in survival for a wide array of malignant diseases, lethality remains high in most cancers and side-effects are severe, including developmental impairment when used in childhood malignancies, infertility as well as damage to non-malignant tissues with resulting diminished quality of life for a large proportion of survivors.

Recently, the realisation that several tumour types contain rare populations of cancer stem cells (CSCs) which are capable of reforming the tumour upon transplantation while their progeny are not, have opened the possibility of using CSCs as targets for directed molecular therapies that could lead to improved tumour eradication, as well as reduced side-effects of treatment.

The goal of the present project is to perform a thorough characterisation of AML, cALL and breast cancer CSCs, as well as a systematic comparison of these with their normal stem cell and progenitor counterparts, using gene profiling to identify putative molecular targets in CSCs. In parallel, we will use mouse genetic modelling to obtain information about genes regulated by oncogenic changes in stem and progenitor cell populations. Directly oncoprotein-regulated CSC targets will be validated *in vitro* and, where relevant, *in vivo.* The final outcome will be identification of the nature and hierarchical position of CSCs in three major cancers, and a set of identified and validated CSC molecular targets with activity against the effects of leukemogenic oncoproteins on hematopoietic stem cell/progenitor populations.

Problem

Human tumours are currently treated primarily with drugs with cytotoxic effects against proliferating cells. This therapy is efficient against cells with the properties of rapidly proliferating progenitors. However, the realisation that many tumour types contain malignant cells with stem cell properties, in that they are able to initiate and sustain a tumour but proliferate infrequently, provides a potential explanation for the ability of many tumours to recur even after the eradication of the bulk tumour mass. The ability to identify and pharmacologically target these cancer stem cells would significantly enhance the efficacy and reduce the side-effects of cancer therapy.

Aim

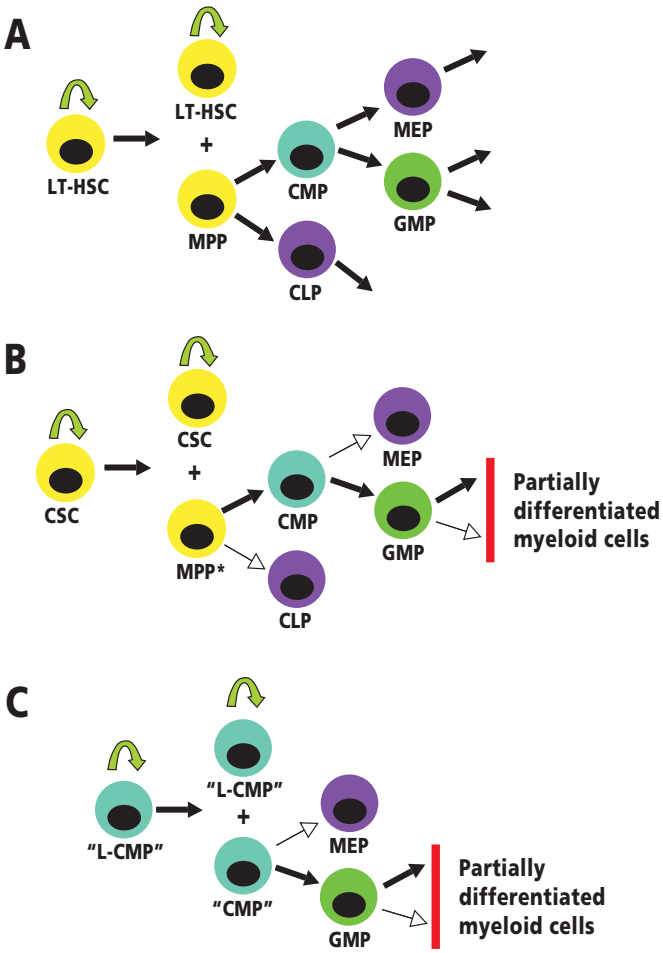
We will use functional analysis and gene profiling of purified human cancer stem cells and genetic modelling in the mouse to identify molecular targets that may be used to selectively eradicate or inactivate the malignant stem cells that sustain tumours. These targets will be validated by knockdown and genetic ablation in mouse model systems. Finally, we will initiate the identification of lead compounds with activity against these targets.

Expected results

We expect to identify and validate target molecules with activity against cancer stem cells in AML, call and breast carcinoma.

Potential applications

These results are directly applicable to the development of drugs targeting human cancer stem cells.



The Cancer Stem Cell hypothesis: Human tumors contain cells that are able to re-initiate tumor formation at distant sites (when metastases form) or when tumors relapse after chemotherapy. As illustrated in the Figure using acute myeloid leukemia as an example, these Cancer Stem Cells are self-renewing (CSC; panel B), and may phenotypically resemble the normal self-renewing stem cells (Long-term hematopoietic stem cells; LT-HSC; panel A) of the tissue from which they arise. However, Cancer Stem Cells may also have phenotypes of more committed progenitors (as exemplified by the leukemic Common Myeloid Progenitor, or L-CMP; panel C), which have acquired ectopic self-renewal capacity, and thus able to perpetuate the malignant clone. Both normal and cancer stem cells reside at the top of a differentiation hierachy; however, while normal stem cells maintain the tissue by providing the cells which sustain its function Cancer Stem Cells give rise to defective progeny that when allowed to accumulate can lead to tissue failure.

LT-HSC: Long-term hematopoietic stem cell; MPP: multipotent progenitor; CLP: common lymphoid progenitor; CMP: common myeloid progenitor; GMP: granulocyte-macrophage progenitor; MEP: megakaryocyte-erythroid progenitor.

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Project website
www.embl-monterotondo.it/research/projects/nerlov/eurocsc.html

Keywords | Apoptosis | cell death | cell imaging | tumour models | kinase inhibitors | pharmacophore inhibitors | scaffold inhibitors |

GROWTHSTOP

Identification, development and validation of novel therapeutics targeting programmed cell death in tumours

Summary

Mounting evidence indicates that the acquired ability to resist apoptosis is a hallmark of most, and perhaps all types of cancer. As scientists learn more about how apoptosis is thwarted by cancer cells, they are also gaining a greater understanding of why many tumours are resistant to the apoptosis-inducing effects of radiation and chemotherapy. These insights will guide efforts to overcome treatment resistance and offer important clues about new drugs that target genes and protein products in the apoptosis pathways to encourage selective cell death.

GROWTHSTOP is exploring how apoptosis is regulated and how it can be selectively triggered to induce suicide in cancer cells while sparing normal cells. The GROWTHSTOP Consortium applies a combination of high resolution bioimaging techniques, proteomics, cellular models, and *in vivo* tumour models towards:

- the understanding of the pathways that signal apoptosis in solid tumours;
- their validation as viable targets for tumour suppression or regression in animal models *in vivo*;
- the discovery and validation of a novel, alternative class of inhibitors that specifically targets protein interactions rather than, or in addition to, enzyme activity. The goal of the GROWTHSTOP project is to exploit apoptotic pathways as a viable therapeutic strategy.

Importantly, more than 30 % of the applied EU budget will be reserved for SMEs that deliver expertise and chemical screening in order to ensure a rapid translation of novel screens and assays into an efficient search for specific drugs manipulating pro-apoptotic pathways.

Problem

Cancer is a major challenge to European health care. Each year nearly two million people are diagnosed with cancer in the EU, and over one million deaths result from this disease. Each case can have a tremendous impact on the health and wellbeing of the affected person, his or her family and personal environment. In addition, a high percentage of cases have major economic impacts, both for the individual and for the health care provider. As a result, improvements in cancer therapy remain of prime importance for the wellbeing of Europeans and for the future development of the Union.

Cancer is caused by mutations in a relatively small and identifiable number of genes, which fall into two categories: proto-oncogenes, which provide critical proliferative or survival signals to cells and which are inappropriately activated by mutation during tumourigenesis; and tumour-suppressor genes, which restrain cell growth and proliferation, and which are lost or inactivated by mutations during the development of a tumour.

Importantly, mutations in individual genes do not cause tumours, since the human genome harbours failsafe mechanisms that protect normal cells from the consequences of deregulated proliferative *stimuli.* Two such failsafe mechanisms are known. The first is an irreversible growth arrest, termed cellular senescence, which is activated by deregulated oncogenic signals through the Ras pathway: one key example is the often lifelong lack of proliferation of melanocytic naevi despite the presence of mutations in B-Raf, a downstream effector of Ras proteins. The second is apoptosis, or programmed cell death, which is activated by many forms of de-regulated proliferative signals. Tumours can only develop when secondary mutations that disable these failsafe programmes arise; as a consequence, many mutations that are found in human tumours are involved in pathways that control either senescence or apoptosis.

Aim

Strategies that aim at restoring these failsafe programmes, in particular apoptosis, in established solid tumours have emerged as an important approach to cancer therapy. The promise of this approach is that such strategies create a therapeutic window, killing tumour cells while sparing normal cells. The key aim of this project is therefore to devise, test and implement strategies that restore apoptosis as a failsafe programme to solid human tumours.

X-ray diffraction of target drug complexes at high resolution.

Project number
LSHC-CT-2006-037731

EC contribution
€ 3 531 507

Duration
48 months

Starting date
01/10/2006

Instrument
STREP

Project website
www.cemit.at/growthstop

More specifically, the following aims will be addressed:

- advanced cancer mouse models, hepatocellular carcinoma and squamous cell carcinoma (SCC) will be used to dissect the contribution of individual kinase pathways to the survival of tumour cells;
- understanding of the signalling mechanisms used by human tumours to counteract apoptosis will be improved;
- a lucid and structured pathway to exploit these findings for therapeutic intervention will be provided, by addressing the problems that hinder the efficient translation of knowledge about kinase pathways into therapeutic approaches.

Expected results

Through the integrated approach of the project, the following results are expected:

- an understanding of the pathways that signal apoptosis in solid tumours;
- their validation as viable targets for tumour suppression or regression in animal models *in vivo*;
- and the discovery and validation of a novel, alternative class of inhibitors that specifically targets protein interactions rather than, or in addition to, enzyme activity, with the final goal of establishing the manipulation of apoptotic pathways as a viable strategy for cancer therapy.

Potential applications

Proliferative diseases.

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Keywords | Cancer biology | high-throughput screening | RNA interference screening | knowledge-based cancer therapy |

INTACT

Identification of novel targets for cancer therapy

Summary

Despite intensive worldwide research efforts, cancer remains a devastating, often poorly treatable disease. We propose to develop and apply new functional genomic technologies that will provide unique approaches to the design of new pathway-specific cancer therapies. To reach the objectives outlined below, we have formed a multidisciplinary research consortium, including top scientists with extensive experience in developing innovative genomics technologies and with an excellent track-record in identifying key signalling molecules involved in cancer, as well as SMEs with experience in identifying cancer-relevant genes and in screening chemical compound libraries. The location of most of the partners at leading European cancer centres will ensure optimal conditions for the development of novel cancer-specific treatments. This proposal provides new possibilities of 'translating basic knowledge of functional oncogenomics into cancer diagnosis and treatment' in compliance with the main goal in the LifeSciHealth call in the Sixth Framework Programme.

Problem

The availability of the complete human genome sequence has provided unparalleled opportunities to examine changes in both DNA sequence and gene expression in normal and cancer cells. Several major projects are underway to identify cancer specific mutations by largescale sequencing or cancer specific alterations in gene expression by micro-array technology and providing important information. However, these technologies have severe limitations in that they provide only an inventory of cancer-associated alterations without shedding light on the functional implications of these changes. Delineating how, or even whether, the alterations identified through these methodologies play a real role in malignant development will be a massive task. We are therefore proposing to make use of the most advanced technology developed within the groups of the programme to move a step further and apply new high-throughput functional screens for the swift identification of new targets that are critical for survival of tumour cells carrying distinct, frequently occurring gene defects. Building on the expertise of other members of the programme we will be able to validate these targets in *in vivo* mouse and human xenograft models, which closely mimic the human disease condition and form the basis for new experimental intervention-intervention strategies.

Aim

The scientific and technological objectives are:

- use large-scale functional genomics, in particular genome-wide lossof-function screens, to identify novel mechanisms, including novel oncogenes and tumour suppressor genes, involved in the development of human cancer;
- to generate novel tools in the form of RNAi retroviral libraries (mouse and human), cell-based assays, mouse models and reagents that will be distributed on a non-profit cost-charge to academic researchers in the European Community;
- to develop novel technologies for target validation in mouse and to develop mouse models to validate the role of the identified genes in the development of cancer;
- to develop cell-based assays for cancer-relevant genes that will serve as a starting point for the identification of anti-cancer agents through the screening of chemical compound libraries. At the end of the four-year programme, collaboration with large pharmaceutical companies will lead to further refinement of lead-compounds and the possible introduction of novel anti-cancer agents into clinical trials;
- to develop novel technologies to study gene function *in vitro* and *vivo,* and to distribute these technologies within the consortium and subsequently to researchers in the European Community.

Expected results

Translating basic knowledge of functional oncogenomics into cancer diagnosis and treatment. Until now, genomic information has been used mainly to develop expression array technologies. Such technologies have been commercialised and are being applied in many laboratories; indeed, members of this consortium have published key profiling papers on several human tumours. The central weakness of this approach is that expression profiling gives no indication of gene function and is, therefore, not suited for the functional annotation of the human genome. As such, expression arrays have been useful in defining prognostic profiles for multiple forms of cancer: however, they have rarely given insight into potential therapeutic strategies for disease.

In contrast, the technology platforms developed by this consortium aim immediately at the determination of gene function on a genomewide scale. Two key technological developments form the basis of this consortium. First, scientists in this consortium have developed retroviral screening technologies to allow phenotypic screens that have specific cellular or organismal phenotypes as read-out. Genes are therefore annotated by their contribution to specific cellular phenotypes. Within this consortium, these screens will be adopted to specific cancer pathways

using pathway-specific reporter cell lines. Therefore, genes are screened at high throughput and are annotated immediately by their functional contribution to individual cancer pathways. Second, the development of RNAi screens and bar-code screens will allow us to conduct for the first time systematic loss-of-function screens in mammalian cells.

Using these technology platforms, the work carried out in this consortium addresses all three key aims of this specific topic: it will help to identify novel potential oncogenes and tumour suppressor genes and will provide insights into the role of telomere shortening and genomic stability (p53) in tumour biology. Most importantly, however, it fills a key technological gap in the identification of novel targets for tumour therapy. The identification of strong dominant oncogenes like bcr-abl has subsequently led to spectacular successes in the development of drugs that specifically target the mutated gene product. Thus, as highlighted by the paradigm drug Gleevec, insights into the molecular pathways that control cancer development can lead to the development of highly cancer-specific drugs. In recent years, it has become clear that disruption of a limited number of tumour suppressor pathways, such as the TGF-β, pRB, the p53 or the APC pathways, is causal for the development of most human tumours. However, findings drugs that specifically target cancer cells with disruption of any of these pathways has been much more difficult to achieve. Clearly, current technologies are unable to identify drug target genes on a genome-wide scale. The technology developed in this consortium addresses this need and will allow the systematic identification of two classes of genes:

First, we will identify genes that show synthetic lethality with disruptions in known tumour suppressor pathways. Synthetic lethal genes are genes whose disruption by themselves cause little or no phenotype, but become lethal in the presence of a second mutation. The existence of this class of genes as well as the feasibility of using them as targets for anti-tumour strategies is clearly documented: for example cells transformed by Myc, in contrast to normal cells, critically depend on the presence of anti-apoptotic genes for survival. Inhibition of anti-apoptotic genes therefore selectively kills Myc-transformed cells. However, a systematic way for the identification of synthetic lethal genes for tumour suppressor pathways is at present not available. The development of resources required to identify synthetic lethal genes for human tumour suppressor pathways on a genome-wide scale is the first key aim of this consortium. Using this technology, the consortium will specifically identify and subsequently validate those genes that will cause lethality in the presence of a disrupted p53, APC or TGF-β pathway. These genes define the key entry points for rational drug development of most solid tumours.

Secondly, RNAi technology, in combination with reporter screens, will identify novel genes that control downstream effector functions of tumour suppressor pathways. Such genes (for example novel regulators of the p15Ink4b gene) will identify novel entry points for targeting cancer pathways. Specifically, the aim of the analysis is to identify candidate genes that allow the restoration of tumour suppressor function in the presence of inactivating mutations. The inclusion of RNAi libraries and bar code screens will ensure that the analysis identifies negative regulators of tumour suppressor pathways. Such genes will provide immediate candidates for drug screening approaches.

Potential applications

This consortium will develop novel high-throughput technologies for the functional annotation of the human genome and will apply these technologies to develop novel therapies to treat human cancer. We believe that these technologies allow us to address a key problem of translating current cancer research into therapy and thus our work in collaboration with SMEs will pave the way for more efficient development of knowledge-based cancer therapeutic intervention.

Project number
LSHC-CT-2003-506803

EC contribution
€ 8 200 000

Duration
48 months

Starting date
01/01/2004

Instrument
IP

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Keywords | Kinases | pediatric pancers | new drugs |

KidsCancerKinome

Selecting and validating drug targets from the Human kinome for high risk paediatric cancers

Summary

Selecting and validating drug targets from the human kinome for high risk pediatric cancers. KidsCancerKinome will make a comprehensive analysis of the human protein kinase family. Protein kinases are already excellent targets for many small inhibitory molecules and antibodies designed for adult tumors.

Six aggressive childhood tumors (neuroblastoma, medullobblastoma, rhabdomyosarcoma, osteosarcoma, Ewing tumor, acute lymphocytic leukemia) will be addressed, which are responsible for 50 % of childhood cancer deaths. Viral shRNA libraries will be applied to test the entire human kinase gene family for tumor-driving kinases in cell lines. They will subsequently be analyzed for mutations and functional parameters in large cohorts of tumor samples. siRNA mediated inactivation in larger cell line panels will critically validate suitable kinases as drug targets.

Novel kinase inhibitors being developed for adult oncology will be tested for *in vitro* activity against the tumor-driving kinases. When no inhibitor is available, a novel generation of siRNA based nucleic acid drugs (LNAs) will be applied. Successful compounds will be taken further to *in vivo* validation in established xenograft models of the six childhood tumor types.

Problem

Each year 15 000 European children are diagnosed with cancer and 25 % die of this disease. Survivors frequently suffer from late side-effects of current treatments regimes.

Translational research of childhood tumors to identify molecular targets for novel generations drugs is therefore urgently needed. In addition, novel targeted drugs currently developed for adult tumors have to become available for children. Indeed, the EU launched in 2007 a paediatric Medicines Regulation to stimulate drug evaluation in children. Nine European research centers devoted to molecular-biologic and pharmacologic studies of childhood cancers and two SMEs therefore engaged in the KidsCancerKinome project.

Aim

The overall aim of the KidsCancerKinome project is to systematically explore the human kinase family for targeted therapy development for children with cancer can be broken down in the following objectives.

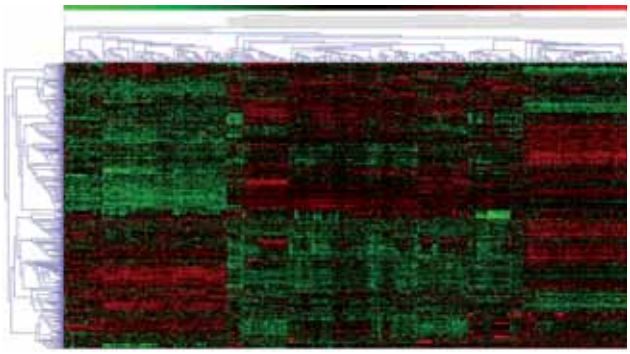
- *In silico* analysis of the ITCC microarray database (in which we established the expression profiles of 600 childhood tumours), for expression profiles of all protein kinase family members. The expression patterns will be used to prioritize the analyses of the protein kinases.
- Functional high-throughput screening of the full >500 member kinase gene family for essential protein kinases in 24 childhood cancer cell lines, using a kinase-specific viral siRNA library and bar-coding-based read out system.
- Screening of extended cell line panels of the six selected tumour types for dependency on known cancer-related protein kinases and the protein kinases identified in step 2, by single-kinase siRNA.
- Mutation analysis of 'tumour-driving' protein kinases (identified in steps 1-3) in series of paediatric tumour samples.
- Analysis of large clinical series of tumour samples for presence and activation status of protein kinases identified in step 1-3 by immunohistochemistry.
- *In vitro* testing of available small molecules for inhibition of the protein kinases identified in step 1-3.
- *In vitro* testing of LNA kinase inhibitors for protein kinases identified in step 1-3 for which no small molecule drugs are available.
- Validation of selected small molecule and LNA kinase inhibitors in nude mouse transplants of childhood tumours.
- Pharmacokinetic and pharmacodynamic studies of LNA's for protein kinases selected in step 1-7 to identify LNA antagonist kinase inhibitor for the drug development pipeline of Santaris.

Expected results

KidsCancerKinome will contribute to a better understanding of the unique pediatric tumor biology and to the development of new drugs.

Potential applications

Identification of new drugable targets and development of new specific treatments for childhood malignancies.



Expression of human kinases in 6 pediatric malignancies (neuroblastoma, medulloblastoma, rhabdomyosarcoma, osteosarcoma, Ewing tumours and acute lymphoblastic leukemias).

Project number
LSHC-CT-2006-037390

EC contribution
€ 3 415 414

Duration
36 months

Starting date
01/11/2006

Instrument
STREP

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Keywords | Lymphangiogenesis | angiogenesis | gene therapy | inflammatory diseases | lymphedema | tissue ischemia |

Lymphangiogenomics

Genome-wide Discovery and Functional Analysis of Novel Genes in Lymphangiogenesis

Summary

Lymphangiogenomics is an Integrated Project with 14 participating consortium members. Its aim is to dissect the processes of lymphangiogenesis thoroughly and to compare them with angiogenesis at the genetic, molecular, cellular and functional levels.

Aim

The aim of this project is to discover novel genes important for lymphatic vascular versus blood vascular development and function, and to study the functional role and therapeutic potential of their gene products in lymphangiogenesis using state-of-the-art technologies.

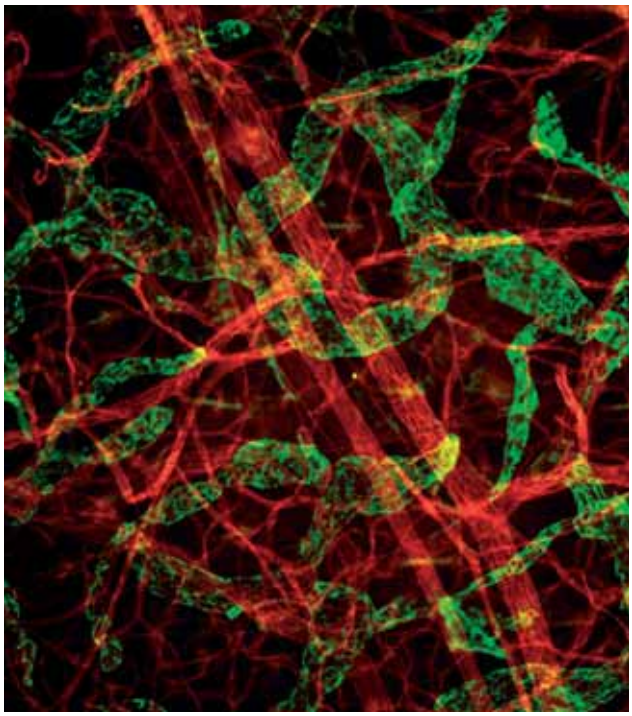
Expected results

These studies will provide a new and fundamental understanding of the molecular and cellular basis of lymphangiogenesis and therefore enable scientists to develop therapies to suppress the growth of lymphatic vessels (for example for cancer and inflammatory diseases) or to stimulate their growth (for example for tissue ischemia and lymphedema).

Lymphangiogenomics puts forward ambitious and competitive research objectives addressing biological processes of high medical importance using a multidisciplinary analysis and validation approach.

Potential applications

Novel therapies for cancer, inflammatory diseases, lymphedema and tissue ischemia.



Lymphatic vessels in a whole mount preparation of the mouse ear skin are visualised with antibodies to LYVE-1 (green). Blood vessels are stained with PECAM-1 antibodies (red).

Project number
LSHG-CT-2004-503573

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€ 9 000 000

Duration
60 months

Starting date
01/05/2004

Instrument
IP

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www.lymphomic.org

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Keywords | Breast cancer | metastasis | gene profiling | organ-specific metastasis |

MetaBre

Molecular mechanisms involved in organ-specific metastatic growth processes in breast cancer

Summary

Breast cancer is often accompanied by the development of metastases, particularly in bone, liver, lung, brain or lymph node tissues. The metastases cause a range of symptoms ultimately leading to increased morbidity and mortality. Metastasis is a complex multi-step process and little is known about the molecular mechanisms that direct metastases to form in certain organs in different patients. MetaBre will analyse differential gene and protein expression in primary breast cancers and metastases in order to identify the molecules involved in organ-specificity. These will be investigated as potential novel therapeutic targets and biomarkers for prognosis of organ-specific metastasis in breast cancer patients. MetaBre has research activities aimed at:

- gene profiling and proteomic analysis to identify new molecular targets;
- functional analysis of new targets in *in vitro* and *in vivo* models;
- mechanisms of angiogenesis and invasion;
- organ-cancer cell interactions;
- development of new pharmacological therapies and diagnostic techniques;
- preliminary clinical trials.

MetaBre will develop *in vivo* models for validation of molecular targets and screening of therapeutic molecules. Metastases will be detected *in vivo* with optical imaging of cancer cells transfected with optical reporter genes, and magnetic resonance techniques.

Problem

More than 200 000 women are diagnosed in Europe every year with breast cancer. The lifetime risk of developing breast cancer is currently one in ten and the disease is the leading cause of death in women between the ages of 35 and 55. There has been considerable success in the treatment of breast cancer in recent years, if detected in its early stages. However, breast cancers are prone to metastasise and cause secondary lesions in bone, liver, lung, brain and lymph nodes. Once solid metastatic tumours are established, the likelihood of complete remission reduces and, depending on the site of metastases, they can cause considerable pain and increased mortality.

Metastasis in breast cancer is a complex multi-step process. Genetic changes in tumour cells give rise to aggressive metastatic cells, and their subsequent development in specific sites depends on a web of cellular and matrix interactions within each organ microenvironment. Understanding the key molecular mechanisms of these metastatic processes can lead to improvements in the prognosis and treatment of breast cancer patients.

Aim

MetaBre aims to discover new gene and protein markers, which can be used for diagnosis as a signature of metastasis to specific organs, and also be targeted for therapy. To achieve this, the partners will analyse samples of breast primary tumours and metastases, with due care of the ethical aspects, as well as established breast cancer cell lines. MetaBre will also study genes and molecules that are already suspected of involvement in metastasis. This builds on previous work of the partners and will enhance understanding of the role of these molecules in metastasis, as well as identifying new opportunities for development of therapies and diagnostic methods.

Expected results

MetaBre aims to generate the following results:

- identification and characterisation of molecular signatures including serum biomarkers for diagnosis of organ-specific metastatic potential in breast cancer;
- identification of new molecular targets for inhibition of angiogenesis, invasion of metastatic cells, and growth of metastases in specific organs;
- development of a catalogued collection of primary tumours, metastases and related samples;
- development of new clinically relevant *in vitro* and *in vivo* models for study of metastatic disease in breast cancer;
- development of diagnostic techniques and identification of at least one novel pharmacological therapy.

Potential applications

The project will identify novel molecular mechanisms that may be targeted for therapy of metastatic disease in breast cancer. The genes related to organ-specific metastasis may be used as biomarkers for stratification of breast cancer patients according to the risk of developing metastases, either through gene expression microarray analysis of primary tumours, or through measurement of those markers present in serum.

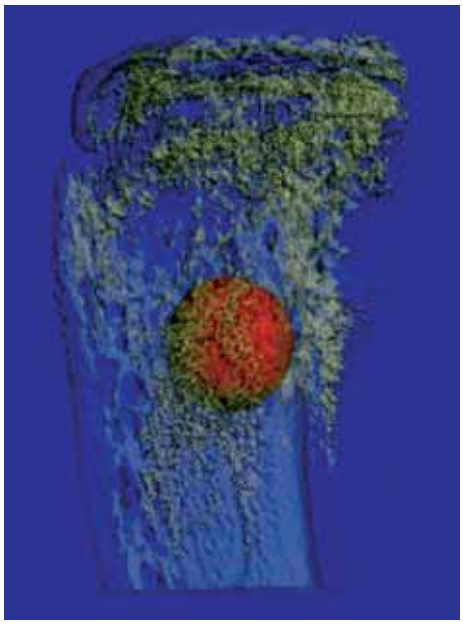

Image of a bone metastasis obtained by 3 dimensional computerised micro-tomodensitometry.

Project number
LSHC-CT-2004-503049

EC contribution
€ 4 005 295

Duration
48 months

Starting date
01/01/2004

Instrument
STREP

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Keywords | Mitosis | phosphorylation | RNAi | mass spectrometry | chemical inhibitors |

MitoCheck

Regulation of Mitosis by Phosphorylation – A Combined Functional Genomics, Proteomics and Chemical Biology Approach

Summary

The proliferation of cells depends on the duplication and segregation of their genomes. The latter is an immensely complex process that remains poorly understood at a molecular level. Mistakes during mitosis contribute to cancer, whereas mistakes during meiosis that cause aneuploidy are the leading cause of infertility and mental retardation. During mitosis, sister DNA molecules are dragged towards opposite poles of the cell due to their prior attachment to microtubules with opposite orientations (bi-orientation). Bi-orientation involves dissolution of the nuclear membrane, changes in chromosome organisation, and re-organisation of the spindle apparatus. How mitotic cells coordinate these disparate but inter-locking processes is poorly understood. One thing, however, is certain – protein kinases like Cdk1 have fundamental roles. Nevertheless, Cdk1's actual function remains mysterious, despite recognition of its importance by a Nobel Prize. The same is true for other mitotic kinases, such as Plk1 and Aurora A and B. We need to know what set of proteins are phosphorylated, what their functions are, or how phosphorylation changes their activity.

Identification of kinase substrates has been hampered by difficulties in mapping phosphorylation sites, in experimentally controlling protein kinase activity, and in evaluating the physiological consequences of defined phosphorylation sites. The premise behind this proposal is that all three hurdles can be overcome by new technologies, namely the use of RNA interference to identify, in a systematic (functional genomics) manner, potential substrates, iTAP-tagging to purify protein complexes, small molecules to inhibit specific kinases in a controlled fashion, and mass spectrometry to identify phosphorylation sites on complex subunits. Because the concept behind this project could be applied to other areas, it will have an impact on European cell biology far beyond the cell cycle community.

Problem

Better understanding of mitotic process in mammalian cells.

Aim

The objectives of this project are:

- to identify all human protein complexes required for mitosis;
- to analyse how these complexes are regulated through phosphorylation by mitotic kinases;
- to evaluate the potential of mitotic kinases as diagnostic or prognostic markers in clinical oncology.

Expected results

- A list of mammalian proteins that have important roles during mitosis.
- Subunit composition of the mitotic protein complexes and their mitosis-specific phosphorylation sites.
- Expression profiles of mitotic kinases in tumour samples and the potential of the mitotic kinases as diagnostic or prognostic markers in clinical oncology.
- A web-based database.

Potential applications

Our basic understanding of the cell division process at a molecular level will be advanced.

The project will generate knowledge relevant for diagnostics and biomarker research as well as for target identification for new antiproliferative pharmaceuticals.

We will develop genomics and proteomics technology, applicable not only to mitosis research but also to other research areas, and we will contribute to the integration and international visibility of the European research area.

Project number
LSHG-CT-2004-503464

EC contribution
€ 8 578 177

Duration
48 months

Starting date
01/04/2004

Instrument
IP

Project website
www.mitocheck.org

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Keywords | Therapy | genome | telomerase | diagnosis | drugs |

MOL CANCER MED

Developing molecular medicines for cancer in the post-genome era

Summary

The cellular immortality enzyme telomerase (one of the most promising universal cancer markers) and associated telomere maintenance mechanisms represent novel anti-cancer targets of enormous therapeutic and diagnostic potential. In MOL CANCER MED, a multinational EU translational cancer research consortium has been established, in which expert cancer geneticists and molecular biologists will interact with prominent pharmacologists, clinicians and pathologists to develop these exciting new cellular targets into measurable pre-clinical advances, within a four-year time-frame.
The project has been structured into three, highly interactive areas of activity, involving the fundamental evaluation and pre-clinical validation of:

- telomerase as a target for cancer treatment and diagnosis based on new molecular knowledge about its expression and function;
- associated downstream telomere maintenance mechanisms as additional targets for novel drug design;
- new anti-cancer drugs based on these targets. The consortium will bring to bear diverse and complementary technological know-how of considerable power to deliver the above primary objectives. Effective management will maximise synergies across MOL CANCER MED in order to produce genuine improvements in the design of new treatments that promise to be active against a broad spectrum of common human malignancies.

Problem

Cancer is a leading cause of death in the western world, second only to cardiovascular disease, and is therefore a European public health problem of overwhelming human and economic significance. The incidence of cancer is set to increase substantially with demographic and possibly environmental influences playing a part. However, there is now an improved molecular understanding of the key genetic, biochemical and cellular changes leading to cancer, in significant part due to the efforts of diverse groups of world-class EU-based scientists. With the completion of the human genome sequence imminent, it is now timely to initiate a major European coordinated effort to translate fundamental scientific knowledge about cancer into safer, more effective, therapies and improved early diagnostic procedures.

MOL CANCER MED is focused on a single group of highly promising anti-cancer targets associated with telomerase and telomere maintenance. Repression of telomerase in the somatic tissues of humans, and probably other long-lived mammals, appears to have evolved as a powerful protective barrier against cancer. Immortalisation *in vitro* of normal human cells that lack telomerase involves the reactivation of telomerase or, rarely, an alternative (ALT) mechanism for maintaining telomeres. It is clear that telomerase is obligatory for continuous tumour cell proliferation, clonal evolution and malignant progression. Because telomerase is found in around 90% of human cancers and is essential for the continued proliferation (and clonal evolution) of cancer cells, it represents one of the most exciting anti-cancer targets thus far discovered. Results with a variety of telomerase inhibitory strategies in human cancer cells have confirmed that its functional inactivation results in progressive telomere shortening, leading to growth arrest and/or cell death through apoptosis. Promising candidate small molecule inhibitors are beginning to emerge that will form the basis for anti-telomerase drug development. MOL CANCER MED is based on successful Framework 5 research concerned with establishing the value of the cellular immortality enzyme telomerase as an anti-cancer target (Project: QLG-1999-01341; TACIT) and represents an expansion and elaboration of this. TACIT yielded results that have triggered new translational research with clearly defined clinical applications. To this set of activities have been added carefully selected new EU research teams, notably in the area of drug development.

Aim

The principal aim of MOL CANCER MED is to fully exploit the results of recent fundamental advances in understanding the role of telomerase and telomere maintenance mechanisms in human cancer development, in order to achieve genuine clinical benefit (i.e. in developing both improved diagnostics and anti-cancer therapies). The principal measurable objectives of the project, over the complete 48 months period, are:

- to validate further the potential of telomerase and telomere maintenance systems in cancer therapy and diagnosis;
- to identify novel molecular targets based on telomere structure, function & stability, that may be of value in treatment and diagnosis of the common human cancers;
- to create a programme of novel small molecule drug development based initially on recently identified (but thus far poorly exploited) targets and, later (from month 12 onwards) exploiting completely new targets identified during the project.

Expected results

- Novel anti-cancer drug targets and diagnostic methodologies derived from advances in:
  - the understanding and definition of biochemical response pathways underpinning the telomere checkpoint for somatic cell proliferation;

- the identification and molecular/functional characterisation of natural mechanisms of telomerase repression and cell self-renewal (including hTERT repressor genes and chromatin remodelling factors) in normal human cells and their dysregulation in human cancers;
- understanding the mechanisms of action and pharmacological activity of existing small molecule telomerase inhibitors (eg BIBR1532);
- establishment of the precise roles of telomere aggregates and telomere-length-independent functions of telomerase in human cancer.

- An advanced molecular understanding of telomerase regulation at chromosome ends (eg involving the key telomere-binding proteins POT1 and hEST1A) and a comprehensive evaluation of such proteins as anti-telomerase drug targets.
- New and effective molecular inhibitors (eg siRNAs, ribozymes and peptide nucleic acids) of telomerase and telomere maintenance (targeting hTERT transcription and telomere-related proteins discovered within the MOL CANCER MED consortium) for the purpose of vasli.
- Panels of new molecular markers of telomerase repression, telomere maintenance and associated signalling pathways, that can be developed into precise, rapid assays for use in novel 'kits' for early cancer diagnosis and prognostic evaluation.
- An understanding of the differential effects of telomerase/telomere maintenance inhibition on normal human tissues and in cancers using organotypic *in vitro* human cell models.
- Rational design of libraries of novel small molecule compounds for screening against new targets, and selection of small molecule antitelomerase/telomere maintenance drug leads active against individual new targets discovered during the course of MOL CANCER MED.
- Identification of potential anti-cancer drugs from the above, following biochemical, pharmacological and functional (*in vitro* and *in vivo*) anti-tumour assays.
- Preclinical exploitation of potential novel cancer drugs through interface with clinical oncology centres and SMEs.

Potential applications

The emphasis of the LIFESCIHEALTH Priority is very firmly placed upon multidisciplinary translational research, in which fundamental scientific knowledge is harnessed for the specific purpose of generating, within the timeframe of FP6, reagents, treatments and diagnostics that are of clinical value. In MOL CANCER MED, a highly focused strategy will be adopted towards applying molecular genetic knowledge about the mechanisms underlying the cancer process to the development of completely new approaches to cancer treatment, eg in bringing molecular biology, cell biology, genomics and target evaluation together with small molecule drug discovery.

Project number
LSHC-CT-2004-502943

EC contribution
€ 4 000 000

Duration
48 months

Starting date
01/10/2004

Instrument
IP

Project website
www.brunel.ac.uk/research/molcancermed/

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Keywords | Multiple myeloma | cancer stem cell | clonal disease progression |

MSCNET

Myeloma Stem Cell Network: a translational programme identifying and targeting the myeloma stem cell

Summary

Multiple myeloma (MM) is a disease where malignant plasma cells accumulate in the bone marrow. Normal plasma cell development at this site is thought to reflect a synchronous terminal differentiation of B cells that have followed sequential stages of maturation. In MM, however, disease characterisation has revealed a number of phenotypic and molecular features that suggest the existence of a clonally related 'less mature' cell, and the question arises whether this may be a stem cell critical to propagating disease.

To address this, the MSCNET has formulated a strategy which includes genomic and proteomic approaches, in order to examine the nature of the cell underlying MM disease origins and progression. This will utilise both *in vitro* and *in vivo* models of the disease, and examine MM at presentation and during its advance, in order to track factors governing disease behaviour in this regard.

Problem

MM is at present an incurable disease, for which effective new therapies are being actively sought. It is by no means clear, however, what the nature of clonal propagation is in MM. To progress work in this area, the MSCNET has set out to identify the nature of the cell underlying disease survival and persistence.

One of the most striking concepts emerging in cancer biology is a role for cancer stem cells (CSCs) in feeding malignant cell growth and tumour maintenance. By definition, these CSCs have an indefinite self-renewal potential, and are able to populate both their own pool and the growth of the tumour. Although the first indication that such a cell might exist came from studies in leukaemia, evidence for CSCs in solid tumours lends further support for the concept of a myeloma stem cell. The question for the MSCNET is whether such a stem cell exists in MM.

Aim

Based on the above hypothesis, the aims will be:

- to study whether the putative myeloma stem cell (MSC) exists as a less differentiated clonally related memory B-cell or as a more mature plasma blast/plasma clonogenic cell;
- to identify genes of potential impact on stem cell function;
- to propose new therapeutic strategies.

Expected results

The results of the scientific programme are expected to redefine stem cell characteristics and especially to characterize the myeloma stem cell compartment and its progeny, as well as its relationship to the tumour micro-environment. This insight will allow us to examine whether there are any MSC-related features that can be targeted by future specific therapies to ablate malignant disease.

Potential applications

Identifying the nature of the MSC will have a profound impact on our understanding of pathogenesis, not only for MM but for all malignant B-cell diseases. Importantly, the MSCNET is well placed to identify potential drug-based approaches to attack MSC and disease progression.

Project number
LSHC-Ct-2006-037602

EC contribution
€ 2 734 000

Duration
36 months

Starting date
01/11/2006

Instrument
STREP

Project website
www.myeloma-europe.org

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Keywords | p53 tumour suppressor | mutations | gain-of-function | p53 status | clinical outcome | mutant p53-reactivating drugs | novel cancer therapy |

Mutp53

Mutant p53 as a target for improved cancer treatment

Summary

Mutations in the p53 tumour suppressor gene are the most frequent genetic alteration in human cancer, occurring in over 40 % of all cases of cancer. One well-studied outcome of these mutations is the loss of the tumour suppressor activity of the wild type (wt) p53. However, there is growing evidence that many of the mutations that occur in the p53 protein generate mutant p53 proteins (mutp53) have acquired new biochemical and biological properties. Through this gain of function (GOF), mutp53 is believed to contribute actively to the cancer process.

We propose to explore mutp53 as a target for novel anti-cancer therapies. Such therapies should aim to either abrogate the GOF effects of mutp53, or restore wt-like properties to mutp53, so that it can now regain its tumour suppressor capabilities. A multi-disciplinary approach will be undertaken to explore and exploit the contribution of mutp53 to cancer.

One component of this project will investigate in depth the molecular properties of mutp53: structural studies will pinpoint the changes that particular mutations inflict on the structure of p53, and allow the classification of mutp53 into distinct subclasses. In parallel, biochemical studies will explore the mode of action of mutp53 within cells, including its impact on patterns of gene expression, identification of specific DNA sequences targeted by mutp53, and discovery of mutp53-interacting cellular proteins. Preclinical models for mutp53-driven cancer will also be developed, as a critical instrument for pre-clinical studies.

The other component will aim at translating this wealth of information into better cancer therapy. One avenue will address the clinical relevance of particular p53 mutations in human cancer, particularly its impact on the patient's response to chemotherapy. This should lead to guidelines for more effective use of conventional therapy. The other avenue will explore novel therapies targeted at mutp53 and mutp53-expressing tumour cells. A major effort will focus on the discovery of small compounds that can restore wtp53-like activity to mutp53. An innovative approach to immunotherapy directed against mutp53-overexpressing cancer cells will also be explored. Owing to the extremely high frequency of p53 mutations, the success of this project will impact on a very large number of cancer patients in Europe and worldwide.

Problem

Cancer is a major cause for human suffering in Europe as well as elsewhere in the world. It causes immense effects on the cancer patients themselves, on their families, as well as on society at large. In addition to the severe human suffering and their immediate societal impact, cancer treatment and management is also a major economic burden. The importance of this problem and the urgency of the need for novel approaches to cancer management and treatment have been recognised by the EC, as reflected by the establishment of a specific call in the area of 'Combating Cancer'.

Mutations in the p53 tumour suppressor gene are the most frequent genetic alteration in human cancer, occurring in over 40 % of all cases of cancer. We propose to explore mutp53 as a target for novel anticancer therapies. Such therapies should aim to either abrogate the gain of function (GOF) effects of mutp53, or restore wt-like properties to mutp53, so that it can now regain its tumour suppressor capabilities. A multi-disciplinary approach will be undertaken to explore and exploit the contribution of mutp53 to cancer.

Aim

In our proposed project, we introduce a multidisciplinary approach to explore mutp53 as a new target for innovative treatment.

A primary objective of the 'Combating Cancer' initiative is 'to combat cancer by developing improved patient-oriented strategies… to better treatment with minimal side-effects' with a focus on 'encouraging the development of evidence-based guidelines for good clinical practice'.

Our project meets these requirements in at least two distinct ways:

- We aim to improve the use of contemporary chemotherapy through providing better guidelines based on correlations between p53 genotype of the tumour and its response to particular types of anti-cancer drugs. It is important to keep in mind that, although novel therapeutic approaches are very exciting and promising, millions of cancer patients all over Europe are being treated every day with standard chemotherapy. Beyond its limited efficacy, this is also associated with significant toxicity and therefore often unjustified patient suffering. The ability to make better predictions as to which particular chemotherapeutic regimen is most likely to work for a particular patient thus has far-reaching implications, both in ensuring better and more effective treatment and, not less importantly, in preventing unnecessary suffering from severe side-effects in cases where it is clear that a particular treatment is not going to work.

Providing new recommendations to oncologists, allowing them to 'individualise' the chemotherapy course chosen for a given patient, will therefore meet the objective of better treatment with minimal side-effects, and will provide evidence-based guidelines for good clinical practice.

- A major component of this project is aimed at developing novel therapies, based on mutp53 knowledge to be gained by the consortium. The increased selectivity and specificity of such drugs is most likely to reduce side-effects on normal patient tissue, because such tissue does not express any mutp53, unlike the targeted tumour cells. Thus, any successful drug that comes out of this project is highly likely to lead to improved clinical practice and to better treatment, with reduced side-effects as compared to the presently available options. Moreover, the fact that close to half of all human tumours possess mutp53 in abundant amounts makes any new drug emanating from this endeavour potentially valuable to a very large number of cancer patients. Such drug, if successful, may thus have far-reaching impacts, not only on individual cancer patients, but also on European society as a whole.

Expected results

The proposed project will address the following main objectives:

- elucidate the biochemical basis for mutp53 GOF (GOF), with special emphasis on genomics and proteomics approaches;
- evaluate the contribution of mutp53 to the malignant properties of cancer cells;
- explore in depth the structural properties of selected mutp53 proteins, in order to provide leads for structure-based rational drug design;
- evaluate the impact of mutp53 status on the response of selected types of human tumours to chemotherapy, and use this information to formulate guidelines for more effective use of currently available anti-cancer therapies;
- search for molecules and compounds that can selectively interfere with mutp53 GOF or restore wtp53 activity to mutp53, and explore them as potential anti-cancer drugs;
- initiate clinical trials (Phase I) with one mutp53-selective drug that has already gone successfully through pre-clinical studies;
- generate leads and new tools towards the development of mutp53- based immunotherapy.

Potential applications

Cancer represents one of the most severe health problems in the European community. Cases are growing with the age of the population. The economic and emotional burden is enormous. Mutp53 protein is expressed in about 50% of all human tumours. In some categories with growing incidence, e.g. lung cancer, colon carcinoma and skin tumours, more than 60-70% of the tumours are associated with mutated p53. This may be due to the induction of p53 mutations by dietary and environmental carcinogenic insults, which are encouraged by modern western society's lifestyle (exposure to sun, very heavy smoking in most parts of Europe, high-fat diet).

In some types of cancer, expression of mutp53 appears to be particularly highly correlated with the more aggressive tumour stages. Yet, in many cancers, mutation of p53 appears to occur during the very early steps of carcinogenesis. This is particularly true for cancers of the lung, head-and-neck, bladder, skin and oesophagus. In these pathologies, mutp53 is amongst the earliest tumourigenic changes that can be detected in the patient, sometimes ahead of the clinical diagnosis of a cancer lesion. The expression of mutp53 is relatively easy to diagnose, employing immunohistochemical assays that are already available as commercial kits and are in use in many pathology laboratories throughout Europe. However, there is still a lack of rapid, low-cost and sensitive assays for mutation detection, and this is the key to the systematic implementation of mutp53-based strategies for cancer diagnosis, prognosis, and treatment. This is why one of the activities of our consortium will be to support the validation and the transfer into production of a new type of micro-array developed by Asperbio, an SME partner of our consortium. Improved detection of p53 mutations may enable earlier cancer diagnosis, increased curability and reduction in the societal impact of cancer morbidity and mortality.

An effective novel treatment of cancers expressing mutp53 could help to prolong life expectancy and quality of life. Such a treatment may be applicable for eradicating small lesions in pathologies where mutation is an early event, thus providing low-cost, low-stress approaches for lesions that are currently managed through surgery and/or chemotherapy. On the other hand, mutp53-based therapies can be applied synergistically with conventional therapy regimens in patients with advanced cancers. The mutp53-based approach thus opens a whole range of possibilities that can be implemented in current medical practice without costly equipment, infrastructures or extensive training programmes.

Development of effective anti-cancer therapy for mutp53-expressing tumours would lower direct and indirect costs by reduction of surgery and intensive care, reduction of duration of medical survey, reduction of emotional burden for patients and their family and faster reintegration of patients as part of the working economy. In addition, one should keep in mind that although novel anti-cancer therapies are a very exciting avenue, millions of cancer patients in Europe are presently being treated with conventional chemotherapy. Current chemotherapy has severe adverse effects on the quality of life of the treated patient. The combination of data from experimental model systems and the cancer patient mutp53 database might potentially identify groups of patients who are not suitable for particular types of contemporary chemotherapy. Better tools to decide which patients should be treated and which to be left untreated are extremely important in reducing the suffering of those patients who will not benefit from the currently available cancer therapy modalities.

Project number
LSHC-CT-2004-502983

EC contribution
€ 8 000 000

Duration
60 months

Starting date
01/02/2004

Instrument
IP

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www.mutp53.com

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Keywords | Vector | nano-sciences | protein-based drugs |

Nano4Drugs

An Innovative Protein-Based Drug Delivery Device using Fluorescent Diamond Nano-Particles

Summary

Advances in genomics have resulted in the development of new protein-based drugs and this trend will increase in the next decade. However, delivery technologies for these drugs must be designed to surmount biochemical and anatomical barriers to safely permit their passage to an intended site.

The targeted delivery of protein-based drugs is limited by a series of barriers and advances made to overcome these barriers will lead to the development of new, safer and more effective drugs by reducing undesirable side effects. To this end, the Nano4drugs consortium has integrated top-level teams across Europe to develop an innovative, challenging, frontier biotechnology device ideally suited for the targeted delivery of protein-based drugs.

The device consists of biocompatible non-bleachable fluorescent diamond nano-particles that can be grafted with both cell-penetrating peptides and protein-based drugs.

As a proof of concept, Nano4drugs will target microtubules in two different biological contexts, neuron and cancer. The protein-based drugs will consist of anti-microtubules peptides recently discovered by one team in Nano4Drug, and of new ones that will be tested during the project with the help of a post-genomic computer-based system of choices designed to guide and improve the development of protein-based drugs.

At the end of this STREP, Nano4Drugs will provide Europe with a better understanding of ways to overcome protein-based drug delivery barriers. In achieving its objectives, Nano4Drugs will also deliver new potential treatments for societal health diseases such as neurological degenerative diseases and cancer.

Problem

A series of barriers limits the targeted delivery of newly developed protein-based drugs, of which three are of critical importance:

- transport of protein-based drugs across the cell membrane;
- understanding the inter and intra-cellular routes taken by protein-based drugs;
- exploitation of the 3D structure of the target, to narrow the protein-based drug specificity, a condition to develop new, safer and more effective drugs by reducing undesirable side effects.

Aim

Nano4Drugs intends to exploit the exceptional properties of diamond nano-particles to develop a novel delivery technology that should overcome these barriers.

Expected results

The cargo will be made of a stable, biocompatible traceable diamond nano-particle of a small size (< 25 nm) with selected surface functional groups able to form an oriented covalent or reversible complex with the protein-based drugs.

As a proof of concept, we will use this new vector to target microtubules which are main critical intra-cellular components involved in major biological processes, such as cell proliferation or neuronal axonal transport.

Potential applications

Protein-based drug delivery in the context of cancer therapy (microtubules are key components for chromosome segregation at the end of mitosis) and neurodegenerative diseases that imply microtubules (for example Alzheimer and spastic paralysis).

Project number
LSHC-CT-2005-019102

EC contribution
€ 2 453 000

Duration
36 months

Starting date
01/01/2006

Instrument
STREP

Project website
www.nano4drugs.com

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Keywords | Drosophila | breast cancer | colorectal cancer | mammospheres | crypt | tissue array | larval neuroblast | sensory organ precursor |

ONCASYM

Cancer stem cells and asymmetric cell division

Summary

An intense line of current investigation into cancer is based on the connection between tumourigenesis and stem cell biology. Some tumours may originate from the transformation of normal stem cells, at least in the case of blood, breast, skin, brain, spino-cerebellar and colon cancers. In addition, tumours may contain 'cancer stem cells', rare cells with indefinite potential for self-renewal that drive tumourigenesis. Interestingly, the same signalling pathways (TGF-beta/BMP, Wnt and Notch pathways) appear to regulate self-renewal in stem cells and cancer cells.

Self-renewal occurs through the asymmetric cell division of stem cells, which thereby generate a daughter stem cell and another daughter cell that contributes to populate the developing organ or the growing tumour. In one of the best understood asymmetric cell division models, the Drosophila nervous system, asymmetry is mediated by a biased Notch-dependent signalling event between the two daughter cells.

ONCASYM partners have recently shown:

- that the process of biased signalling during asymmetric cell division is controlled by endocytosis;
- that tumours can be induced in mutants with altered stem-cell asymmetric division. In human normal and cancer stem cells, asymmetric cell division is supposed to take place, but it has not directly been proven yet. Furthermore, the role of biased signalling by endocytosis in these stem cells has not been addressed to date.

The aim of this project is threefold:

- to screen for genes involved in asymmetric cell division of human cancer stem cells;
- to characterise the asymmetric cell division of these stem cells by using these candidate genes as markers;
- to study functionally the role of the identified candidate genes during asymmetric cell division of cancer stem cells. Our ultimate goal is to untangle the molecular machinery of cancer stem cell asymmetric division, thereby providing druggable targets for cancer therapy.

Problem

Cell types within a tumour vary in their ability to form the whole tumour mass. In fact, only very few cells can give rise to all cells present in the tumour. These so-called tumour stem cells have been characterised in a variety of tumours, including leukaemia, breast cancer and brain tumours. Their existence challenges conventional tumour therapy, which is targeted at destroying rapidly proliferating cells. Stem cells often proliferate slowly and might not be eliminated by such therapies, which might explain the high relapse rate observed for some cancers. Alternative therapies that target stem cells are not available. This is partly due to our limited understanding of proliferation control in stem cells and the lack of appropriate cancer models which mimic the development of tumours from defined stem cell populations.

Aim

The goal of this project is to develop new therapeutic strategies that target tumour stem cells. Stem cells are characterised by their ability to divide asymmetrically and thereby form self-renewing and differentiating daughter cells at the same time. Even a slight change in the balance between these two cell types could dramatically increase the number of daughter cells created by a stem cell and thereby contribute to tumour formation.

Expected results

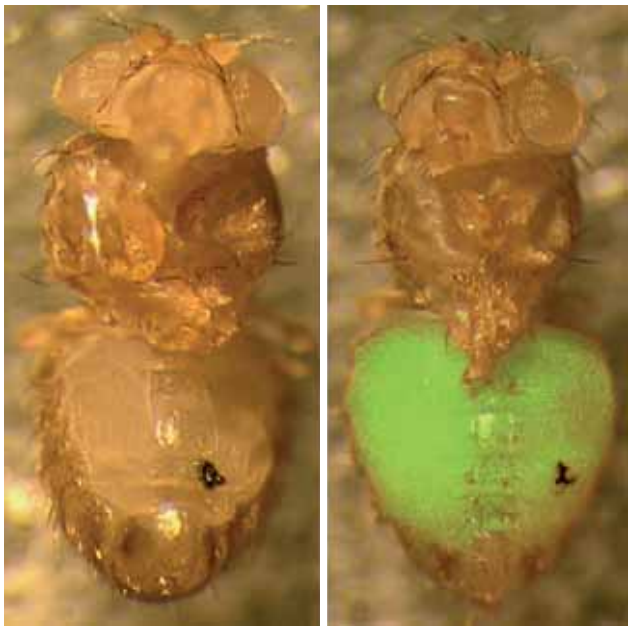
In our project we plan:

- to discover the genes involved in asymmetric cell division and tumour suppression in normal and malignant stem cells, using Drosophila as a model system, and to find their human and mouse homologues;
- to use this candidate gene list to find markers for the identification of normal and cancer stem cells in the mammary gland and the intestinal crypts and use these markers to image the asymmetric cell division event.

Potential applications

We will directly translate the acquired knowledge into the clinical practice.

- We plan to validate the newly identified 'stemness' signature as a clinical tool for genomic grading and prognostic evaluation. This task will be initially accomplished by retrospectively performing meta-analysis, using the currently available public databases as well as the wide collection of cases from our tumour registry.
- Tissue microarrays will be used to further validate the relevance of candidate 'stemness' genes to the diagnostic routine, by establishing their predictive strength in relation to the common clinical-prognostic parameters.
- Prospectively, the identified 'stemness' genes will be introduced as 'biomarkers' for the clinical and prognostic evaluation of cancer patients enrolled in *ad hoc* clinical trials at the European Institute of Oncology, even including their use in the procedure of the sentinel node in order to identify the presence of stem cells in metastasis.



Drosophila as a model system for tumourigenesis. Transplanted tissue into Drosophila abdomen (black scars) do not cause tumours (labelled in green) unless the transplanted tissue is mutant for factors involved in asymmetric cell division (right fly). ONCASYM uses this assay as a gene discovery tool for the genes involved in tumourigenesis.

Project number
LSHC-CT-2006-037398

EC contribution
€ 2 823 800

Duration
36 months

Starting date
01/10/2006

Instrument
STREP

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Keywords | TRAIL | Ras | CRC-colorectal cancer | PI3K | DISC | choline kinase | aurora inhibitors | caspase-2 | mitochondria | mouse models |

ONCODEATH

Sensitisation of solid tumour cells to death receptor-related therapies

Summary

TNF-related apoptosis-inducing ligand (TRAIL) is currently a promising anti-tumour agent with proven activity on several cell and animal cancer models. A unique feature of TRAIL is its specificity towards malignant cells while sparing normal cells. At present, preclinical studies with recombinant TRAIL are in progress as well as with an anti-TRAIL-R2 monoclonal antibody with no hepatotoxicity. In order to identify specific cell death determinants induced by KRAS, BRAF and PIK3CA oncogenes, examination of specific pathways like B-RAF, MEK, PI3K, Rho, and BCL-2 will be performed. Studies will be further extended to animal models of tissue-specific K-ras-induced carcinogenesis.

Combined action of TRAIL with other therapeutic molecules will be utilised, in order to succeed optimum effects with minimum concentrations and toxicity. The potential findings of our study will be determined by the present research project and will provide mechanistic basis for a pharmacogenomic approach which could be further therapeutically exploited, in order to provide cancer patients with novel personalised therapies in the near future.

Problem

In the last decade, an encouraging decline of the death rate from cancer has been observed, as a result of recent advances in prevention, early diagnosis and therapy. Efforts are made towards the generation of 'smart' anti-cancer drugs that will target specific molecules, depending on the molecular phenotyping of the patient's tumour.

Aim

- Panel on new cell lines with up- and down-regulated colon cancer-related oncogenes.
- Map of TRAIL-induced proximal signalling pathways per system.
- Determinants of caspase-2 activation and Bax in TRAIL-induced apoptosis of tumour cells.
- Assessment of a role of mitochondrial fission and fusion in TRAIL-mediated apoptosis.
- Selection of PI3 kinase and Aurora inhibitors that cooperate with TRAIL in inducing apoptosis of colon cancer cells.
- Assessment of sensitivity of tumours induced by activated oncogenes in transgenic mice and in mouse xenografts.

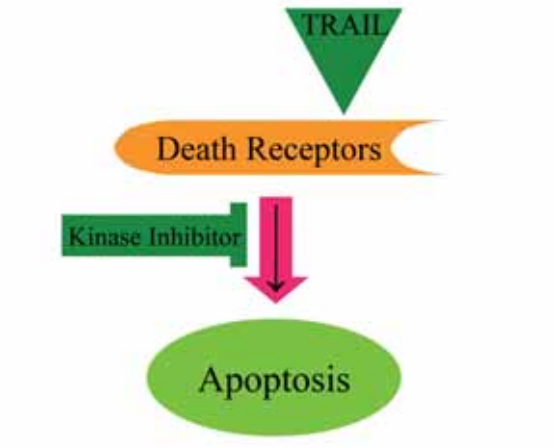
Expected results

We believe that the principal objective of our project is reachable, for the following reasons. The novelty and innovative potential of the ONCODEATH project is based on the strength of its partners, a highly efficient management and organisation plan, and a novel technology development strategy: all of these address R&D possibilities for cancer therapy, which derive from very recent findings for the role of additional mutations in colorectal cancer formation, as well as that the fact that tumours have intrinsic defective apoptotic pathways, like 'Achilles' heal', that can be exploited per case.

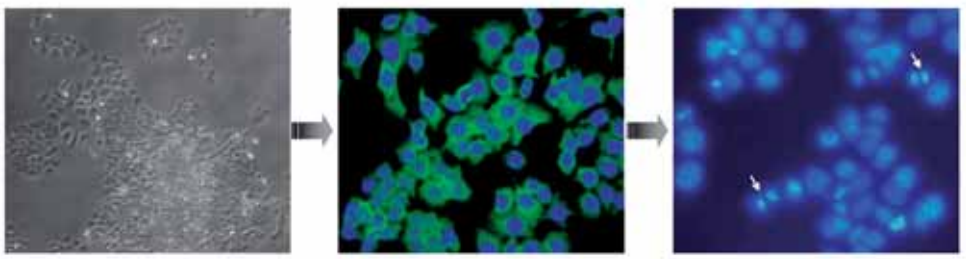
ONCODEATH can offer possibilities to test novel signalling drugs alone and in combination with a very potent apoptotic ligand TRAIL, in order to enhance potency and overcome resistance/non-responsiveness of tumours and finally induce tumour-selective death.

Potential applications

We will investigate resistance of pathways to apoptosis present in tumour cells and we will aim to sensitise these to cell death by treatment with a combination of agents. These pathways will be studied by genomic technologies, imaging technologies, biochemistry, tumour biology and novel therapeutic agents which are prepared on specific target and pathway inhibition. The analysis will be performed on representative cell as well as mouse models for colorectal carcinogenesis. Specific oncogenic mutations will be analysed according to the research plan described. If successful, the efforts should provide landmark discoveries in the field, which would greatly advance our current knowledge and exploitation of defective apoptotic pathways in tumour cells.



Incorporation of various inhibitors to help overcome possible kinase resistance to TRAIL induced apoptosis.



Normal cell growth and epithelial like morphology are severely altered once cells enter apoptosis.

Project number
LSHG-CT-2006-037278

EC contribution
€ 2 344 900

Duration
36 months

Starting date
01/11/2006

Instrument
STREP

Project website
www.eie.gr/nhrf/institutes/ibrb/eu-projects/oncodeath/index-en.html

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Keywords | Prostate cancer | androgen receptor | bone metastasis | high-throughput target identification and validation | high-throughput low molecular weight compound screening |

PRIMA

Prostate Cancer Integral Management Approach

Summary

Prostate cancer is one of the most common malignancies in the western male population. In Europe, approximately 40 000 men die of prostate cancer each year and, due to the ageing population, that number is likely to increase to around 60 000 men in 2020. Therefore prostate cancer is a significant medical problem with which the European Community will be confronted increasingly in the oncoming decades. For localised prostate cancer, radical therapies, aiming at eradicating all malignant processes in the prostate gland, are available, which can cure the patient. However, if the malignant process has locally or distantly spread, no curative medical intervention is currently in existence. Since the early 1940s, androgen ablation therapy has been the mainstay in an attempt to control prostate neoplasms, but unfortunately this is only of a palliative nature and tumour progression is inevitable, due to the expansive growth of cancer cells that are unresponsive to currently available hormone therapies. Furthermore, prostate cancer cells have a strong tendency to spread to the bone, a site where metastases cause great morbidity, ultimately leading to a painful death.

Problem

There has been little progress in the management of metastatic prostate cancer since Huggins and Hodges proposed endocrine treatment of the disease. It has become clear that the treatment is palliative and not curative. Therefore, new targets for therapy need to be identified, and methods to interfere with these to change the course of the disease have to be developed and tested pre-clinically in (animal) model systems.

Aim

The main aim is the identification of appropriate targets for therapy for advanced prostate cancer. Two hypothesis-driven approaches are combined with target discovery efforts using state-of-the-art, highthroughput, molecular profiling technologies. The identified targets are validated at two levels, i.e. phenotypically and functionally (high-throughput small interfering RNA screens). Once identified, validated targets are used to screen for low molecular weight compounds, which are subsequently tested in animal models for bone metastatic prostate cancer. In the PRIMA project, a multidisciplinary effort is proposed to explore pathways that lead to the most lethal aspect of prostate cancer, i.e. hormone-therapy-unresponsive bone metastatic lesions. It has become clear that in the majority of advanced prostate cancers, the androgen receptor-signalling pathway is active even in the absence of androgens. European research teams with a leading role in androgen receptor research will integrate their efforts to exploit androgen receptor-mediated signalling as a therapeutic target.

This should be achieved by:

- targeting the androgen receptor itself;
- interfering with androgen receptor-activation by non-steroids;
- studying non-transcriptional functions of the androgen receptor;
- targeting essential androgen-receptor co-factors over-expressed in prostate cancer;
- inhibiting those androgen receptor target genes that regulate prostate cancer cell growth, survival and differentiation.

The androgen receptor teams will join forces with European investigators that study interactions between prostate cancer cells and the bone microenvironment.

Expression profiling of members of the transforming growth factor superfamily and signal transduction molecules in cell lines, animal models and clinical specimens should provide more insight into the role of these molecules in the development of bone metastatic lesions. Furthermore, epithelium-mesenchymal transition will be extensively studied. The exploration of pathways leading to hormone therapy-unresponsive bone metastatic disease will use functional genomics and expression profiling as technology platforms. These technology platforms will also be used to identify novel candidate targets for treatment and a specific bioinformatics platform will be developed to analyse all collected data. In the targeted discovery phase, candidate target genes will be identified that, in addition to already available targets from earlier collaborative programmes, need to be phenotypically and/or functionally validated. Phenotypical validation will be performed in archival material of patients with a well-documented follow-up in all stages of the disease process. In addition, high-throughput functional, cell-based analysis and molecular target validation will be performed by knocking down genes that are over-expressed in hormone refractory or metastatic prostate cancers using RNA interference. The knowledge obtained from the targeted discovery phase and validation phase will be used to establish assays, which will, in turn, be used for highthroughput screening of low molecular weight compounds (i.e. more than 25 000 compounds). The assays will use easy-to-upscale formats and reporters that can be easily read out. The final phase of the project will be the testing of interesting compounds for their ability to interfere

Project number
LSH-CT-2004-504587

EC contribution
€ 6 000 000

Duration
60 months

Starting date
01/07/2004

Instrument
IP

Project website
www.primaproject.org

efficiently with cancer cell proliferation and/or survival in a bone environment in the absence of androgens. The lead compounds will be tested for their efficacy in models for bone metastatic prostate cancer. Hence, the translation of the obtained knowledge into therapeutic strategies is an integrated part of the project.

Expected results

We expect to identify 3-5 novel targets that will be pursued for the utility in high-throughput screens of low molecular weight compounds. We expect to identify 2-3 molecules that can be tested in an animal model for bone metastatic prostate cancer.

Potential applications

Treatment of metastatic prostate cancer. Based on the animal models a decision will be made for animal toxicological testing (beyond the scope of this IP) and phase 1 clinical trials. The consortium will start a joint venture with a pharmaceutical company.

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Keywords | Genomics | molecular genetics | transcription factors |

Regulatory Genomics

Advanced Genomics Instruments, Technology and Methods for Determination of Transcription Factor Binding Specialities; Applications for Identification of Genes Predisposing to Colorectal Cancer

Summary

Determination of the sequence of the human genome, and knowledge of the genetic code through which mRNA is translated, have allowed rapid progress in the identification of mammalian proteins. However, less is known about the molecular mechanisms that control the expression of genes. This project sets out to address this problem by developing novel tools and methods for analysing the specificity of transcription factors to bind to particular sequences of DNA.

Problem

Not enough is known about the molecular mechanisms that control expression of human genes, and about the variations in gene expression that underlie many pathological states, including cancer. This is caused in part by a lack of information about the second genetic code – binding specificities of transcription factors (TFs). Deciphering this regulatory code is critical for cancer research, as little is known about the mechanisms by which the known genetic defects induce the transcriptional programs that control cell proliferation, survival and angiogenesis. In addition, changes in binding of transcription factors caused by single nucleotide polymorphisms (SNPs) are likely to be a major factor in many quantitative trait conditions, including familial predisposition to cancer.

Aim

The objective is to develop novel genomics tools and methods for the determination of transcription factor binding specificity. These tools will be used for the identification of regulatory SNPs that predispose to colorectal cancer, and for characterisation of downstream target genes that are common to multiple oncogenic TFs.

The specific aims are:

- to develop novel high throughput multiwell-plate and DNA-chipbased methods for determination of TF binding specificity;
- to determine experimentally the binding specificities of known cancer- associated TFs;
- to predict computationally, and to verify experimentally, elements that are regulated by these TFs in genes that are essential for cell proliferation;
- to develop a SNP genotyping chip composed of SNPs that affect the function of TF-binding sites conserved in mammalian species;
- to use this chip for the genotyping of patients with hereditary cancer predisposition as well as controls in three European populations, for identification of regulatory SNPs associated with cancer.

Expected results

This project aims to understand the basic principles involved in growth regulation by oncogenic TFs, and is expected to have a major impact in the understanding of cancer. Identification of SNPs associated with low penetrance cancer predisposition would be a major breakthrough in the effort to understand inheritance of quantitative trait loci, and will have implications on the population's healthcare.

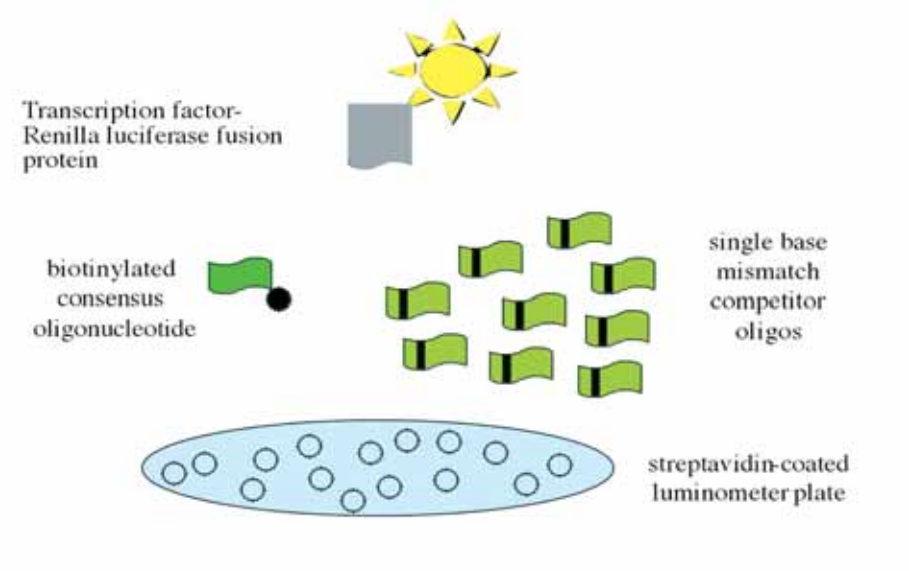
The methods developed within the project (1) have already allowed genome-scale prediction of regulatory elements in the human genome, and the methods developed should make feasible the analysis of DNAbinding specificities of all TFs, and consequently significantly improve our understanding regulation of gene expression.

Potential applications

We expect that the project will lead to the identification of genes that associate with colorectal cancer. This will have direct implications on diagnosis and treatment of a cancer type that affects more than 200 000 Europeans every year.

Methods, tools and instrumentation for advanced genomics developed within this project will improve EU scientific competitiveness in the rapidly developing field of regulatory genomics, and will allow EU scientists to be in a very good starting position to decipher the genetic code controlling regulation of gene expression.

(1) Hallikas O, Palin K, Sinjushina N, Rautiainen R, Partanen J, Ukkonen E, Taipale J, Genomewide Prediction of Mammalian Enhancers Based on Analysis of Transcription-Factor Binding Affinity. Cell. 124:47-59, 2006.



A high-throughput assay of transcription factor binding specificity developed within the Regulatory genomics project (Hallikas et al., Cell 124:47-59, 2006).

Project number
LSHG-CT-2004-512142

EC contribution
€ 2 200 000

Duration
48 months

Starting date
01/09/2004

Instrument
STREP

Project website
research.med.helsinki.fi/regulatorygenomics/

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Keywords | Cancer | ageing | cellular senescence | cell death | DNA damage | telomerase | immunosurveillance |

SENECA

From Cellular Senescence and Cell Death to Cancer and Ageing

Summary

The main objective of the SENECA project is to improve the awareness of ageing research among cancer researchers, stimulating cooperation between the two disciplines. To achieve this objective a conference will be organized to provide a forum for scientific exchange among leading scientists working in the fields of ageing and cancer, as well as to stimulate cooperation aimed at redefining molecular targets and improving cancer prevention and therapeutics in the ageing population. The discussion will focus on such issues as DNA damage, telomeres and telomerase in cancer and ageing, effects of tissue environment in tumour formation, impact of the ageing immune system on cancer immunosurveillance and immunotherapy, links between stem cells and cancer and ageing, links between tumour suppression and cellular senescence, and cellular senescence as a new target in anticancer therapy. Attendance of approx. 300 scientists and representatives of other key stakeholder groups from around the world is anticipated.

Problem

Age is the most important demographic risk factor for many life-threatening human cancers. Over two-thirds of all diagnosed cancers occur in people over the age of 65. According to IARC, worldwide cancer rates increase sharply with age: for the age group 65 years and older incidents of cancer are 2-3 times higher than in the 45-64 age group and 12-36 times higher than in the 25-44 age group. The increased incidence of cancer in elderly people has been related to age-associated changes occurring with time in the whole system. The elderly are more vulnerable than younger individuals to environmental carcinogens not only because of potentially greater exposure time, but for other reasons, including impaired macromolecular repair and defense against reactive oxygen species, age-dependent changes in tissue environment facilitating increased pro-inflammatory status, possibly diminished immuno-surveillance of malignant transformation and pro-cancerogenic activity of senescent cells.

Since tumours include cancer cells with an extensive proliferative history, subject to senescence and senescence-avoidance mechanisms, cancer researchers commonly study various aspects of biological ageing. However, many cancer specialists, clinicians, and industry representatives remain unaware of what ageing research can offer for cancer prevention and therapy. Presently the research fields of biological ageing and cancer in Europe remain largely fragmented, without structured links or widespread interdisciplinary approaches.

Aim

The main goal of the project is to improve the awareness of ageing research among cancer researchers, stimulating cooperative research between the two disciplines. The enhanced cooperation should aim at redefining molecular targets and improving cancer prevention and therapeutics in the ageing population. This goal will be achieved by organizing an international conference for approximately 300 participants October 4-6, 2007.

Expected results

The conference will provide a forum for scientific exchange among outstanding European scientists working in the fields of ageing and cancer. The discussion will focus around such issues as: DNA damage, telomeres and telomerase in cancer and ageing, effects of tissue environment in tumour formation, impact of the ageing immune system on cancer immunosurveillance and immunotherapy, links between stem cells and cancer and ageing, links between tumour suppression and cellular senescence, and cellular senescence as a new target in anticancer therapy. The conference will also bring together other key stakeholder groups such as policy makers, clinicians and industry.

The proposed event will contribute to attracting scientists from cancer research and other disciplines to ageing research. It will help to establish sustainable organizational links between these two closely related scientific fields, structuring European research in oncogerontology.

Potential applications

The planned conference is expected to:

- stimulate cancer specialists to use the insights, results and methodologies stemming from ageing research in studying aetiology, prevention and therapy of cancer, especially in the elderly;
- design strategies as to how basic research results in cancer and ageing can be best transferred into industrial exploitation and clinical practice. This may be an important starting point for the development of new preventive and therapeutic measures. It may give a whole new dimension to geriatric medicine, as it will shift the emphasis from care – which is extremely expensive – to maintenance of function and prevention of disease as long as possible.

Project number
LSSM-CT-2006-037312

EC contribution
€ 142 800

Duration
24 months

Starting date
01/10/2006

Instrument
SSA

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Keywords | RNA silencing | microRNA | RNA interference | short interfering RNA | developmental biology | molecular biology | gene expression |

SIROCCO

Silencing RNAs: organisers and coordinators of complexity in eukaryotic organisms

Summary

RNA silencing is the natural ability of a cell to turn off genes. Only a few years ago it was unknown, but now RNA silencing is one of the most powerful tools available to researchers. Recent discoveries have revealed a previously unknown role for RNA (ribonucleic acid). They have shown how, in addition to the previously understood role as a cellular messenger that directs protein synthesis, RNA can also silence expression of genes. By introducing specific silencing RNAs into an organism, the expression of genes can be turned down in a controlled way. The phenomenon of RNA silencing is thought to have evolved as a defence mechanism against viruses. In primitive cells it was a type of immune system that could recognize and then silence viral genes. Later in evolution the silencing mechanism was recruited for switching off genes involved in normal growth of cells and responses to stress. Small regulatory RNAs (sRNAs) are the mediators of RNA silencing and are important integrators of genetic, epigenetic and other regulatory systems. They are the focus of the SIROCCO programme. sRNAs have been referred to as the dark matter of genetics: a recently discovered mass of molecules that crucially affect the behaviour of the genetic universe through interactions at the RNA level.

Problem

The exploitation of sRNAs offers many opportunities for improving the diagnosis and therapy of human disease and for advances in biotechnology. sRNAs fall into two major classes:

- short interfering RNAs (siRNAs) which are 21-24 nucleotide RNAs derived from long double-stranded RNA;
- microRNAs (miRNAs) which are derived from transcripts containing partially double-stranded stem-loop 'hairpin' structures about 70 nucleotides long. Both are cleaved from their precursor RNA by double stranded RNA-specific endonucleases. One strand of the resulting small RNA is loaded into RNA-induced silencing complex (RISC) that also contains Argonaute (AGO) proteins. Binding to the correct Argonaute protein is necessary for cleavage of the target messenger RNA. siRNAs and miRNAs have been found in a variety of organisms including plants, fruit flies, zebrafish, mice, and humans. sRNAs are also a useful tool in the laboratory, where they can be used to silence gene expression (RNA interference).

Aim

The overall objectives of the SIROCCO project are:

- create catalogues of sRNAs from healthy and diseased cells. Novel sRNAs will be identified through using a combination of bioinformatics and high throughput sequencing;
- determine the tissue- and cell-type pattern of miRNA expression using microarray, RNA blot and *in situ* hybridisation methods;
- fully refine methods for sRNA detection. These detection methods will be enhanced using locked nucleic acid-containing and other oligonucleotide probes, and by modified PCR methods;
- characterise proteins and subcellular compartments required for sRNA processing and activity. At present, there is a foundation of knowledge about miRNAs, but very little is known about siRNAs. Genetic, biochemical and imaging approaches will be used to fully characterise the molecular machines responsible for both miRNA and siRNA biogenesis;
- dissect sRNA regulatory networks. It is known that miRNAs may affect particular target mRNAs but how their activity fits into more complex regulatory networks is poorly understood. Developing this understanding is one of the major objectives of the SIROCCO programme;
- identify rules for sRNA efficiency and specificity. The RNA-silencing efficiency of sRNAs will be determined by assay of sRNAs, their precursors or their DNA in transgenic organisms, in cell cultures or *in vitro*;
- explore delivery methods for sRNAs or sRNA precursors.

Efficient use of sRNAs as pharmaceuticals will depend on the development of methods for their efficient delivery into cells and animals. Current technology uses modified viruses to introduce siRNAs into cells to reduce expression of a target gene. In the later stages of the project, the SIROCCO consortium will initiate research into the suppression of genes implicated in various diseases.

The mechanism of RNA silencing must be thoroughly understood in order to use RNA as a drug without side effects. It is also necessary to understand more about the role of silencing RNAs in normal growth and development. That information will then allow us to use the presence of silencing RNAs to diagnose disease states in a cell.

Somite-specific expression of miR-206.
Mouse embryo (E10.5) was hybridized to an LNA oligonucleotides complementary to miR-206.
The blue staining indicates the very specific accumulation of miR-206 in the somites.
(Wheeler G, Valoczi A, Havelda Z, Dalmay T. In situ detection of animal and plant microRNAs. DNA Cell Biol. 2007 Apr; 26(4):251-5.)

Expected results

The SIROCCO consortium will investigate the stages in growth, development and disease that are influenced by sRNAs. The project can be considered to have three overlapping phases. The first is descriptive and will continue throughout the programme. This phase aims to describe the full complement of sRNAs in a range of organisms and cell types and correspondingly to develop a complete understanding of the proteins that act as enzymes, co-factors and structural components of the sRNA machinery.

The second phase involves testing the function of sRNAs and sRNA-related proteins in the basic sRNA mechanisms, and eventually establishing their role in regulatory networks through experimental intervention. Genetic and molecular methods will be used to manipulate the expression of these components, while biological assays and molecular profiling of RNA will be used to assess the role of the targeting components.

In the third, predictive phase of the programme, the aim will be to develop rules to describe the behaviour of sRNA systems as isolated regulatory modules and as part of complex regulatory networks. Component activities in this phase will involve the computation of rules and their validation by experimentation. It will be possible from this phase to design sRNA mimics of natural sRNAs, and to predict their effects in cells and organisms. It will also be possible to predict the behaviour of cells or organisms in which the sRNA machinery is regulated by developmental or external stimuli.

Potential Application

RNA silencing technology has enormous potential for use as a therapeutic agent in the treatment of infectious diseases and for any condition involving the mis-regulation of gene expression. It is known that different microRNAs can function as tumour suppressors or oncogenes and that their expression levels have diagnostic and prognostic significance. The role of small RNAs in complex neuropathological disorders such as schizophrenia and in neurodegenerative conditions such as Alzheimer's Disease is being investigated by members of the SIROCCO consortium. Diagnostic or therapeutic advances in these areas would have powerful public health implications.

The SIROCCO consortium aims to understand and exploit the diversity of sRNA mechanisms. The elucidation of the genomics of sRNA and of sRNA-based regulation will lead to novel and fundamental insights into the composite genetic networks that underlie normal and diseased growth and development. Achieving these aims will reinforce European competitiveness in fundamental research and innovation and will solve important societal problems relating to public health by improving diagnosis and treatment of diseases.

Project number
LSHG-CT-2006-037900

EC contribution
€ 11 781 445

Duration
48 months

Starting date
01/01/2007

Instrument
IP

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Keywords | Epigenetics | gene regulation | histone modification | small molecule inhibitors | cancer therapy |

SMARTER

Development of small modulators of gene activation and repression by targeting epigenetic regulators

Summary

The identity of a given cell within a metazoan organism is primarily defined by the expression pattern of its genes. The activation and repression of particular genes is tightly regulated by the concerted action of transcription factors that recognize and bind specific DNA sequences within regulatory regions. Work done over the last 20 years revealed this basic mechanism of gene activation and repression, while recent experiments exposed an additional layer of regulation involving modifications of DNA and bound histones. These modifications are involved in cellular inheritance of transcriptional states through cell division and development and as they are not coupled to DNA sequence are referred to as epigenetic. Many factors that impact on epigenetic phenomena are clearly distinct from basic transcription factors and are involved in regulating chromatin structure. Modulation of chromatin structure is frequently achieved by intrinsic enzymatic activities that either mark particular regions within the genome for activity or repression or use the hydrolysis of ATP to remodel nucleosomal arrays. This variation of gene expression patterns in response to external and internal signals has a major influence on stem cell differentiation, the maintenance of tissue integrity and the adaptation of organisms to environmental dynamics. Recently, small molecule inhibitors that target chromatin-modifying enzymes have been used for cancer treatment, which has opened new avenues in therapeutical research. The SMARTER project aims at the development and improvement of such compounds, which is the primary mission of Chroma, the SME participating in the consortium.

Problem

The epigenetic level of gene regulation is being analysed intensively worldwide. However, the knowledge gained from these studies has not been transferred to drugs or drug candidates for the treatment of major diseases. Equally, development of small molecules targeting epigenetic regulators have so far not been the major focus of drug discovery efforts.

To pursue this promising approach it is obviously important to further improve understanding how the eukaryotic genome in general, and the human genome in particular, operates. Therefore knowledge about its DNA sequence, its epigenetic control systems and its dynamic structure in relation to gene expression must be integrated.

Aim

The SMARTER project aims at the development and improvement of compounds targeting epigenetic regulators. These compounds will be tested in various assays making it possible to collect data sets of several parameters as histone modifications, chromatin states, gene expression patterns and physiological characteristics in an integrative manner for the first time.

Therefore major objectives are:

- identification of small molecule inhibitors that target various histone-modifying enzymes;
- validation of these inhibitors through *in vivo* analytics of histone modifications states;
- establishment of histone modification states as standard readouts for drugs that target epigenetic modifiers;
- improvement of known epigenetic modulators through medicinal chemistry;
- identification of target genes that are regulated by the SMARTER molecules;
- application of the SMARTER molecules in standard animal model systems to verify their activity in living organisms.

Expected results

Our proposal will thereby promote the development and improvement of a new branch of cancer drugs and as well support validation of new potential drug target enzymes. Additionally, tools will be generated which allow new insights in fundamental mechanisms of gene regulation by epigenetic modification.

Potential applications

In the context of human health, an understanding of gene regulation is central to our understanding of many medical complaints and conditions. Fundamental aspects of chromatin function are increasingly recognized as important factor in the development of many severe and often untreatable diseases. Therefore many proteins that are involved in the regulation of chromatin structure are potential drug targets and small molecules directed against these factors will play an increasingly important role in treating patients that are affected by one of these maladies.

The cooperation between leading European chromatin labs and Chroma is expected to greatly strengthen the SMEs knowledge base and thereby having a strong impact on its ability to enter drug candidates in clinical trials.

Project number
LSHG-CT-2006-037415

EC contribution
€ 2 500 000

Duration
48 months

Starting date
01/12/2006

Instrument
STREP

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Keywords | Hereditary | tricarboxylic acid cycle | fumarase | succinate dehydrogenase | renal | paraganglioma | leiomyoma |

TCAC in Cancer

Defects in the Tricarboxylic Acid (Krebs) Cycle

Summary

For this project, top European cancer research groups working on the association between defects in the tricarboxylic acid cycle (TCAC) and cancer form a consortium to profoundly characterise the human phenotypes to enable identification and efficient cancer prevention, and to unravel the underlying molecular mechanisms. Recent breakthrough findings by the consortium participants and others have shown that defects in at least four TCAC genes – fumarate hydratase (FH, fumarase), and succinate dehydrogenase (SDH) B, C, and D – can confer susceptibility to cancer. We shall take these studies forward by characterising the natural history of the syndromes in large European materials.

Simultaneously, we shall perform functional studies to elucidate the cellular events induced by these defects by systematic biology approaches including functional studies in cell lines, model organisms, and transcription profiling of TCAC deficient and proficient tumours and models.

TCAC defect-associated expression patterns will be utilised to examine other cancer types for such defects. We have evidence that modifying genes play a key role in TCAC defect-associated tumourigenesis and candidate regions have been identified. Following gene identification, the possible role of these modifiers in low penetrance cancer predisposition in the general population will be examined. The rationale to form this consortium is simple and strong. The consortium brings together the key European cancer researchers studying TCAC-associated tumourigenesis. Studying the tumourigenic effects of FH and the different units of SDH separately would be ineffective, and formation of the consortium will ensure that Europe will maintain the initiative in this new and exciting field of research. The deliverables arising from the work packages will contribute to the common goals; prevention of TCAC-associated cancers and learning the lessons these lesions can teach to cancer research.

Aim

The two key tasks to achieve this project's objective are:

- characterising the natural history and prevalence of TCAC-deficient cancers;
- unravelling the molecular mechanisms driving TCAC-associated tumourigenesis.

Expected results

The impact of the proposed research is two-fold. First, it provides a basis for cancer detection, prevention and treatment in high-risk individuals with TCAC defects. The discoveries by us and others linking TCAC defects to a high risk of tumours are so recent that even the very basic data on the natural history of the respective syndromes is missing and, without this knowledge, evidence-based measures to fight this novel tumour type cannot be developed. Second, the proposed research will create data on the frequency of TCAC-deficient hereditary and sporadic cancers, and will characterise the molecular mechanisms underlying their genesis. This will be a major advancement for cancer research in general.

Potential applications

This project will create data for management of TCAC-deficient tumours.

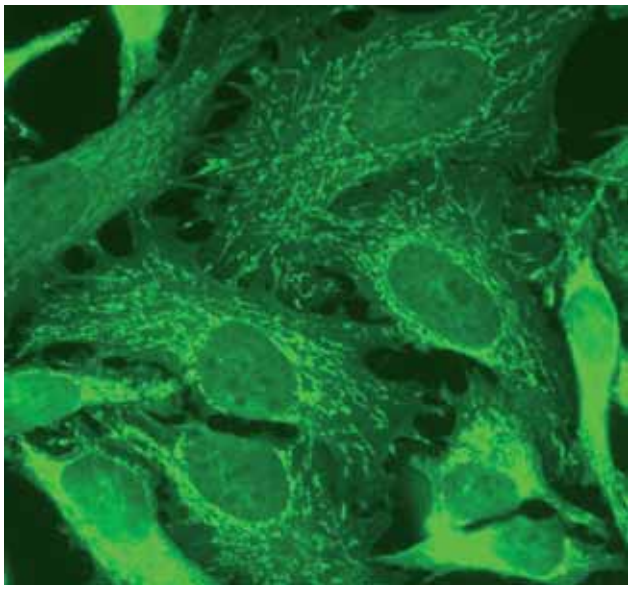
Diagnosis

- Improved molecular diagnosis of hereditary susceptibility.
- Classification of tumours.

Also, it will create an expression profile-based classifier for TCAC deficient cancers.

Management

- Hereditary susceptibility: it goes without saying that an exact diagnosis of the syndromes involved is a very significant factor in improving the management of the patient, and the relatives. Appropriate follow-up strategies and much more accurate genetic counselling on cancer risk will become available.
- TCAC-deficient tumours: whether hereditary or sporadic, TCAC-deficient tumours are likely to display special biological properties which are relevant for clinical management, including response to drug treatment. We anticipate that the more detailed molecular classification of tumours provided by efforts of this proposal will considerably improve the standard care of such lesions.



Immunofluorescence staining of FH in HeLa cells shows strong mitochondrial (and weak cytoplasmic) protein expression.

Project number
LSHC-CT-2005-518200

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€ 2 751 000

Duration
48 months

Starting date
01/01/2006

Instrument
STREP

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Keywords | HSV-1 | hepatocellular carcinomas | oncolytic vectors | targeting |

THOVLEN

Targeted Herpesvirus-derived Oncolytic Vectors for Liver Cancer European Network

Summary

The overall objective of THOVLEN is to develop safe and efficient herpes simplex virus type 1 (HSV-1)-derived oncolytic vectors, designed to strictly target and eradicate human hepatocellular carcinomas (HCC), the most common liver cancer of adults. HSV-1 is certainly one of the most promising viral platforms for the development of improved oncolytic vectors, as anticipated by the unique biological properties of this virus and confirmed by the encouraging results coming from clinical trials in gliomas. However, the first generations of oncolytic HSV-1 vectors have also shown limitations regarding efficacy and safety. New generations of innovative HSV-1 vectors with improved potency and safety are required before the oncolytic strategy using HSV-1 becomes a standard therapeutic reality against cancer, and this is the goal of THOVLEN. One of the most important innovative contributions of our project concerns the overall approach towards the improvement of HSV-1-based oncolytic viruses. Instead of focusing on the development of vectors carrying deletions in particular virus genes, we will engineer competent, but replication-restricted, HSV-1 vectors, strictly targeted to HCC. These vectors will combine multiple HCC-targeting approaches, both at the level of entry and at the level of gene expression and replication, and will be able to multiply and spread only in HCC, while displaying no virulence in normal healthy tissues. Additionally an important innovation is related to the ability of the HSV-1 vectors to permit a sophisticated and flexible combined approach against HCC. That is, in addition to optimising the oncolytic properties of HSV-1 vectors, THOVLEN will exploit the very large transgenic capability of HSV-1 to generate vectors that will simultaneously display multiple and multimodal anti-tumour activities acting either locally or systemically, including combined expression of anti-angiogenic, immune-modulatory and oncolytic proteins.

Problem

Data from epidemiological studies indicate that HCC accounts for 80% of all primary liver cancers and is one of most prevalent malignant diseases worldwide. It is the fifth most common cancer, with an estimated average of about 0.45 million new cases diagnosed each year, and it ranks fourth in mortality rate. Furthermore, the incidence of HCC has increased noticeably over the past two decades and has become progressively associated with younger age groups. Despite development of novel therapeutic methods in recent years, prognosis of advanced HCC remains very poor, with a life expectancy of about six months from time of diagnosis and a less than 3% survival rate for untreated cancer over five years. This disease therefore represents a major challenge for public health in Europe and in the world. It decreases human longevity, impairs citizens' quality of life and represents an immense burden to Europe's healthcare services. New therapeutic strategies are clearly needed to improve this situation. The possibility of developing an anti-cancer therapy whose activity increases with time, while retaining tumour specificity and expressing multiple anti-tumour activities is a new and still uncharted area of cancer therapy and, in this context, the administration of HSV-1 oncolytic vectors shows a considerable promise. Therefore, by developing our project, THOVLEN will ultimately serve to accelerate the development of new, safer and more effective treatments.

Aim

The central goal of THOVLEN is to design HCC-targeted virus vectors that will simultaneously display multiple targeting elements acting at different steps of the virus life cycle, in order to ensure maximum aggressiveness for HCC cells with minimum or no virulence for healthy tissues. In addition, the unique advantage of the HSV genome to carry about 40 kbs of foreign DNA will be exploited in the context of designing a multimodal approach for cancer therapy, required for improvement of the inherent anti-tumour activity of the virus. The availability and the expertise in using several well-defined animal models for liver cancer will allow us to evaluate safety and efficacy of our vectors in relevant systems. Through fundamental research, we will generate novel genomic and proteomic information on the interactions between the oncolytic vectors and the normal and cancer cells, which will guide the rational design of vectors targeted to HCC cells, therefore resulting in the improvement of the vector oncolytic potency, and the improvement of safety.

Project number
LSHB-CT-2005-018649

EC contribution
€ 2 494 460

Duration
36 months

Starting date
01/01/2006

Instrument
STREP

Project website
www.tholven.eu

Expected results

We will investigate different ways of producing HSV-1 vectors conceived to penetrate specifically, express genes and replicate into HCC, therefore killing these cells and allowing the spread of the virus to infect other tumour cells. In addition to their inherent targeted oncolytic potential, these vectors will express enhancing transgenic sequences, encoding immune-modulators, anti-angiogenic molecules, fusion proteins, or toxic proteins, which are expected to have an additive negative action on tumour growth. Our expectation is to produce, by the end of the project, a number of such vectors, combining targeting and enhancing functions, which will be fully evaluated for efficacy and toxicity on different HCC animal models, including standard and transgenic mice, and woodchucks.

Potential applications

Treatment of primary liver cancers (hepatocellular carcinomas).

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Keywords | Apoptosis | autophagy | necrosis | programmed | cell death |

TransDeath

Programmed Cell Death across the Eukaryotic Kingdom

Project number
LSHG-CT-2004-511983

EC contribution
€ 2 500 000

Duration
36 months

Starting date
01/12/2005

Instrument
STREP

Project website
www.transdeath.org

Summary

The project aims to broaden the experimental net to catch regulators of programmed cell death (PCD) by comparative research on diverse organisms that each may be uniquely suited to unravel a type of conserved PCD process. The major approach will be across the eukaryotic kingdom and the main objective will be to understand these types of cell death in humans. TransDeath thereby aims to produce knowledge on genes and biochemical processes that regulate PCD in different organisms, and to apply that knowledge to develop strategies and targets for human disease therapy.

Problem

Programmed cell death (PCD) is normally invoked during development and immunity, but inappropriate PCD is associated with pathologies, including cancer and degenerative diseases. Conserved genes controlling apoptosis, a type of PCD dependent upon caspase proteinases, were first identified in the model organism C. elegans. This work received a Nobel Prize in 2003, and biomedical research has established related mammalian PCD pathways. However, phylogenetically conserved PCD types other than apoptosis exist in animal and non-animal cells. This TransDeath project will focus on cellular and molecular events in these less well-known cell death types.

Aim

The specific TransDeath objectives include:

- characterising the diversity of genes and biochemicals controlling PCD of diverse types;
- functionally comparing these genes and biochemicals between organisms;
- deriving genetic and functional models of PCD evolution.

Expected results

The results of this project should be of value to the European and international scientific communities. Our efforts will strengthen European research in the strategic area of functional genomics and yield information on gene function in PCD immediately relevant to pharmaceutical R&D.

Potential applications

Test genes and biochemicals on PCD related to normal human function and disease.

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Keywords | Metastase | xenografts | tyrosine kinases | biomarkers | tumour profiling | siRNA | animal models | drug design |

TRKCancer

The anoikis suppressor TrkB as a target for novel anti-cancer agents

Project number
LSHC-CT-2006-037758

EC contribution
€ 2 368 715

Duration
36 months

Starting date
01/01/2007

Instrument
STREP

Summary

The failure of anti-cancer therapies generally results from locally intractable invasive growth or from the presence of metastases refractory to treatment with curative intent. A novel therapeutic strategy is to develop new anti-cancer drugs specifically targeting the invasive or metastatic phenotype of tumour cells.

We propose to validate at the pre-clinical level a strategy that targets the critical mechanism allowing apoptosis evasion and survival of invasive or metastatic tumour cells. Anoikis is a process by which a cell detached from its resident tissue undergoes apoptosis as a result of loss of normal cell-matrix interactions. Loss of anoikis allows survival of cancer cells in abnormal micro-environments, such as tissue compartments invaded by the primary tumour, and the intravascular compartment, during the metastatic process. The BDNF receptor TrkB is a potent suppressor of anoikis and is responsible for apoptosis evasion that occurs in aggressive human tumours overexpressing TrkB.

The aim of the present proposal is to validate TrkB as a target for new anti-cancer drugs, aiming to restore anoikis and thereby destroy the invasive and metastatic cancer cells.

Problem

- Metastasis is a cause of cancer relapse.
- TrkB, as an anoikis suppressor, may favour metastasis, but the relevance of this target has not been assessed in relevant cancer models.
- There are no TrkB inhibitors ready for clinical trials.
- Biomarkers of metastasis are lacking.

Aim

- To validate TrkB as a target for anti-metastasis agents by using human tissue-derived animal models.
- To identify novel TrkB inhibitors.
- To explore mechanisms of action of TrkB inhibitors and to identify biomarkers of metastasis.

Expected results

- Novel animal models.
- Novel TrkB inhibitors as potential anti-cancer drugs.
- Novel biomarkers of metastasis.

Potential applications

- Novel anti-cancer agents.
- New diagnostic tools and indices of therapeutic efficacy.

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Keywords | Tumour | host | signalling | stem cell | angiogenesis | lentivirus |

Tumour-Host Genomics

Genome-wide Analysis of Signalling Pathways in Regulation of the Interactions between Tumour and Host Cells: Applications of Cancer Therapy

Summary

In addition to oncogenic mutations that act cellautonomously, tumour cell growth depends on interactions with its microenvironment. The tumour microenvironment consists of cells of haematopoietic and mesenchymal origin, including inflammatory cells, stem and progenitor cells, fibroblasts, endothelial cells and vascular mural cells. Tumour cell growth is known to depend on the interaction of tumour cells with such stromal cells. For example, a growing tumour needs to recruit normal endothelial and vascular mural cells to form its blood vessels. In addition, tumour cells induce stromal cells to secrete factors that contribute to tumour cell growth and invasion. Stromal cell-dependent interactions represent an attractive target for cancer therapy, because normal cells are genetically stable, and would not be expected to develop resistance to therapeutic agents. The development of such therapies is hampered by the fact that the molecular mechanisms behind tumour-stroma interactions are often poorly understood.

In summary, the work plan entails development of novel advanced functional genomic instruments, technologies and methods to study tumour-host interactions in cancer, and to apply these techniques to the identification of molecules and processes in normal cells, which could be targeted by novel anti-cancer therapeutic agents. In addition, we will develop targeted lentiviruses which would allow *in vivo* delivery of therapeutic agents into tumours. Functional validation of the discovered targets and developed delivery systems will be performed in *in vivo* models of murine tumour growth and dissemination. For purely technical reasons, melanoma and prostate cancer models are planned to be utilised first. However, tumour-host interactions are universally.

Essential for the growth and dissemination of any malignant disease, and the results of the experiments will be applicable for any kind of human cancer. The work has significant exploitation potential and relevance for health in the understanding of the molecular mechanisms of tumourhost interactions, and in the treatment of cancer.

Problem

Tumour cell growth depends on interactions with its microenvironment. The development of cancer therapies targeting these interactions is hampered by the fact that the molecular mechanisms behind tumourhost interactions are often poorly understood.

Aim

- To identify endothelial/BM cell-specific cis-regulatory elements for use in lentiviral *in vivo* targeting vectors.
- To develop a targeted lentiviral library for the inhibition of selected major cell signalling pathways.
- To identify tumour-derived factors that lead to increased angiogenesis and recruitment of stromal cells contributing to a microenvironment permissible for tumour growth.
- To identify host-derived factors that induce tumour cell growth and tumour stem cell self-renewal.
- To test *in vivo* the effect of targeted lentiviruses in inhibition of tumour growth and metastasis.

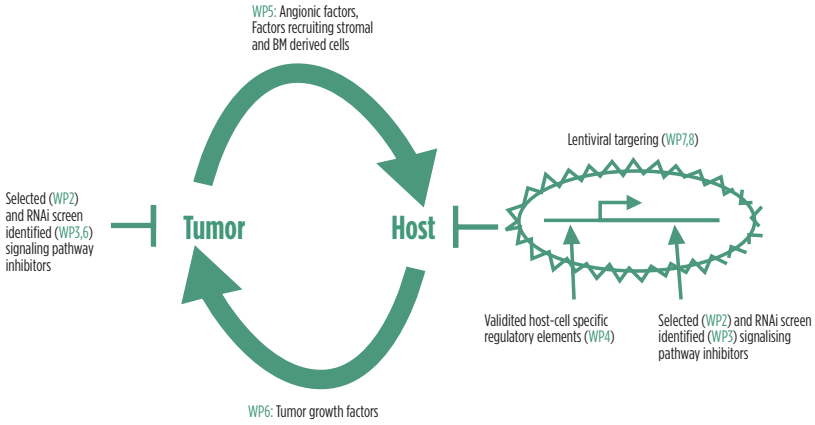
Expected results

The project aims to develop novel tools and methods to study tumourhos interactions in cancer, and to apply these techniques to the identification of molecules and processes in normal cells, which could be targeted by novel anti-cancer therapeutic agents. In addition, we also propose to develop targeted lentiviruses that specifically express genes in bone marrow-derived cells and/or in endothelial cells, which would allow *in vivo* delivery of therapeutic agents into tumours.

Potential applications

Potential target genes for the treatment of cancer will allow the search, and preclinical and clinical validation of respective lead compounds.

Tumour-host interactions are universally essential for the growth and dissemination of any malignant disease, and the results of this project could in principle ultimately be applicable for any kind of human cancer.



Summary of the science and technology objectives of the project, and the work package structure. The project aims to develop novel tools and methods to study tumour-host interactions in cancer, and to apply these techniques to the identification of molecules and processes in normal cells, which could be targeted by novel anti-cancer therapeutic agents. In addition, we will also develop targeted lentiviruses that specifically express genes in bone marrow-derived cells and/or in endothelial cells, which would allow *in vivo* delivery of therapeutic agents into tumours.
Abbreviations: BM, bone marrow; RNAi, RNA interference; WP, work package.

Project number
LSHC-CT-2005-518198

EC contribution
€ 2 700 000

Duration
36 months

Starting date
01/11/2005

Instrument
STREP

Project website
research.med.helsinki.fi/tumorhostgenomics/default.htm

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Aetiology

The uncontrolled cell growth characterising cancer can be initiated by the interaction of human cells with specific agents, on the basis of an individual genetic predisposition. Despite great advances in the understanding of these interactions, our ability to treat tumours remains very low: this is a clear sign that much remains to be learnt.

Human carcinogenesis related knowledge has shown a dramatic increase in its width and complexity over the last few years. In fact, the availability of enhanced and more powerful tools along with a more functional translational approach including valuable *proof-of-principle* feedback from the clinical perspective have created the opportunity to look more closely into the regulatory processes of the cell growth and, once initiated, cancer behaviour (including tissue invasion and metastatic potential).

Not only it is now clear that different regulatory pathways are to be altered in order to create a predisposition for cancer initiation: environmental external factors (biological, chemical and physical agents) seem to have different activities when they act on the cell alone or in combination. The striking evidence that different patterns of gene-to-environment interactions can develop when a population with certain genetic characteristics move from an area of the world to another (as like as the incidence of breast cancer of Japanese people levelling the one of Northern Americans when the former move from Japan to US) add as well a further degree of complexity to the overall.

A quick and reliable identification of agents capable to induce carcinogenesis, along with a better understanding of the genetic substrate on which these environmental factors express their action is ideally coupled with epidemiological and molecular pathology state of the art validated information and preliminary results from clinical experiences. These processes of gathering multidisciplinary enhanced knowledge benefit from a *look forward perspective* towards cancer prevention and treatment strategies.

EU funded projects aimed to better understand cancer aetiology clearly shift towards a pragmatic application of the basic knowledge generated so far and do exploit the whole range of foreseen funding instruments: from the Specific Support Action –SSA- 'AIDIT' aimed at extending the clinical platform of another EU funded initiative (IMPACT) to the Framework Programme Associated and Candidate Countries for the targeted screening of prostate cancer in men with genetic predisposition; to the Specific Targeted Research Project (STREP) 'POLYGENE' aimed at identifying novel key determinants underlying breast and prostate cancer and finally to the large Integrated Project 'CARCINOGENOMICS' aimed at creating a validated high-throughput genomic based test for assessing genotoxic and carcinogenic properties of chemical compounds *in vitro;* the Network of Excellence 'GENOMEL' aimed at understanding the genetic causes (susceptibility) of melanoma and the gene-to-environment interaction, predominantly with the exposition to the sun light and the 'Integrated Project INCA' focused on the role of biological agents capable of inducing chronic infections in the pathogenesis of infection-associated cancers.

Alfredo Cesario

Keywords | Prostate cancer | BRCA1 | BRCA2 | targeted screening | associate candidate countries |

AIDIT

Advancing International Co-operation and Developing Infrastructure for Targeted Screening of Prostate Cancer in Men with Genetic Predisposition

Summary

In the EU, approximately 200 000 men are diagnosed annually with prostate cancer, and this figure is likely to increase due to the ageing population, which will cause a considerable healthcare problem. Inherited genetic factors are important in this disease, for example the breast cancer predisposition genes BRCA1 and BRCA2 have been reported to increase the risk of prostate cancer significantly. The European IMPACT study (scheduled to begin in 2005) aims to put in place networks and infrastructures in 23 countries (18 of them in Europe) to identify a male population harbouring germ line mutations in the BRCA1 and BRCA2 genes, and recruit them into targeted screening programmes for prostate cancer. IMPACT also aims to support future research into the targeted screening and clinical management of prostate cancer in high-risk individuals. The main goal of this proposal (AIDIT) is to stimulate co-operation with Associated Candidate Countries (ACCs) in relation to the IMPACT study. It is intended that a Specific Support Action (SSA) could provide the means to identify and recruit appropriate centres in the ACCs; stimulate the participation of research teams in ACCs and connect expertise in all collaborating countries in this area. Networking and dissemination of the latest results from ongoing prostate cancer screening studies are crucial elements of this proposal, which has the long-term aim of enabling centres in the ACCs to join the IMPACT study, thus establishing a larger consortium and research base. AIDIT is also aimed at raising the profile of the need to improve clinical management of prostate cancer, educating the relevant stakeholders, improving quality of life, reducing early mortality and reducing the financial burden of healthcare. It will consider relevant gender, ethical and societal issues, supporting the implementation of the Sixth Framework Programme and, in particular, the Combating Cancer topic of Thematic Priority 1. AIDIT can only occur under the auspices of an EU SSA.

Problem

Prostate cancer is a common cancer in men but the cause of the disease remains a mystery. There is a potential for improving patient management and for reducing early mortality by targeting screening for prostate cancer. Studies have indicated that BRCA1 and BRCA2 genes significantly increase the risk of prostate cancer but further work is needed in the area to determine the exact risks of this patient population. International collaboration has been established in 23 countries worldwide but out of the Associate Candidate Countries only one centre in Turkey is involved.

Aim

To expand the IMPACT study collaboration into the Associate Candidate Countries through advertising the study both to the general population and to researchers using media, establishing a website and holding an international conference.

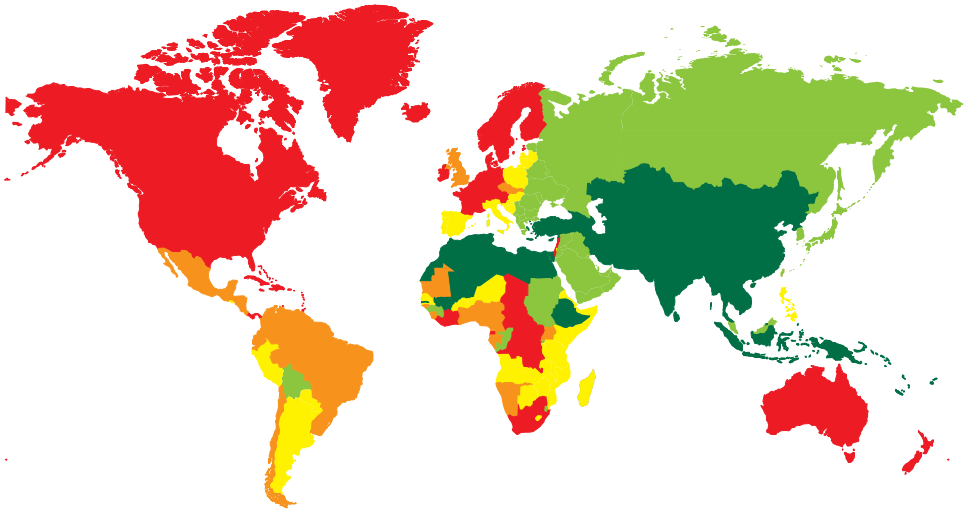
Expected results

- To host an international conference to bring all collaborators together and meet and share knowledge.
- To identify and recruit new centres in ACCs.
- To recruit ACC members onto the IMPACT study, and specialist and steering committees.
- To increase awareness of the BRCA1/2 link to prostate cancer and encourage genetic testing in individuals at risk.
- Development of a centralised website.
- To raise the profile of the need for increased detection of mutations in BRCA1 and BRCA2 in men, and for improved clinical management of prostate cancer in the ACCs.
- To educate the relevant stakeholders through the creation of reliable, informative, and fast communication hardware and software systems.

Potential applications

- Promote future research collaborations between teams in these countries and the current IMPACT consortium.
- To assist in guiding future clinical management of men with BRCA1 and BRCA2 mutations.

INDICENCE OF PROSTATE CANCER: ASR (WORLD) (ALL AGES)



GLOBOCAN (IARC 1998)

Project number
LSSM-CT-2005-018686

EC contribution
€ 330 057

Duration
18 months

Starting date
01/12/2005

Instrument
SSA

Project website
Under construction

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CARCINOGENOMICS

Development of a high throughput genomics-based test for assessing genotoxic and carcinogenic properties of chemical compounds *in vitro*

Summary

The major aim of CARCINOGENOMICS is to develop *in vitro* methods for assessing the carcinogenic potential of compounds, as an alternative to current rodent bioassays for genotoxicity and carcinogenicity. The major goal is to develop a battery of mechanism-based *in vitro* tests accounting for various modes of carcinogenic action. These tests will be designed to cover major target organs for carcinogenic action e.g. the liver, the lung, and the kidney. The novel assays will be based on the application of 'omics' technologies (i.e. genome-wide transcriptomics as well as metabonomics) to robust *in vitro* systems (rat/human), thereby also exploring stem cell technology, to generate 'omic' responses from a well-defined set of model compounds causing genotoxicity and carcinogenicity. Phenotypic markers for genotoxic and carcinogenic events will be assessed for the purpose of anchoring gene expression modulations, metabolic profiles and mechanism pathways. Through extensive biostatistics, literature mining, and analysis of molecular-expression datasets, differential genetic pathways will be identified capable of predicting mechanisms of chemical carcinogenesis *in vivo.* Furthermore, generated transcriptomic and metabonomic data will be integrated into a holistic understanding of systems biology, and applied to build an iterative *in silico* model of chemical carcinogenesis. Subsequently, predictive genetic pathways will be used as the scientific basis to develop high throughput technology for accelerating analysis of genomics responses *in vitro,* indicative for human carcinogenic risk, by a factor of 100. It is expected that the outcome of this project will generate a platform enabling the investigation of large numbers of compounds for their genotoxic and carcinogenic potential, as envisaged under the REACH initiative. This will contribute to speeding the identification of potential harmful substances to man, while lowering costs and reducing animal tests.

Problem

The evaluation of the carcinogenic potential of a compound is currently completely depending on chronic rodent bioassays administering chemicals at maximally tolerated doses. Chemical carcinogens are classified as either genotoxic or non-genotoxic. For the important class of non-genotoxic carcinogens, no suitable test model is available at all. The available mechanistic information is relatively more clear-cut for genotoxic carcinogens, and genotoxicity testing of chemicals is mandated by regulatory agencies worldwide. A four-test battery is required comprising bacterial mutagenesis, *in vitro* mammalian mutagenesis, *in vitro* chromosome aberration analysis and *in vivo* chromosome stability analysis. However, for pharmaceuticals, it has been assessed that these assays in combination predict rodent carcinogenicity correctly by not more than 38% while simultaneously producing high percentages of false positives; the correctness of prediction by the *in vivo* assay appears only 11,5% while the percentage of false positives is 15%. A survey of over 700 chemicals demonstrates that even 75–95% of non-carcinogens gave positive (i.e. false positive) results in at least one test in the *in vitro* test battery. False positive results in *in vitro/in vivo* assays for genotoxicity obviously overrate the necessity of rodent carcinogenicity studies. But also rodent cancer bioassays provide inadequate data to estimate human cancer risk: this creates a significant problem for interpreting the results of animal experiments with carcinogens in relation to humans.

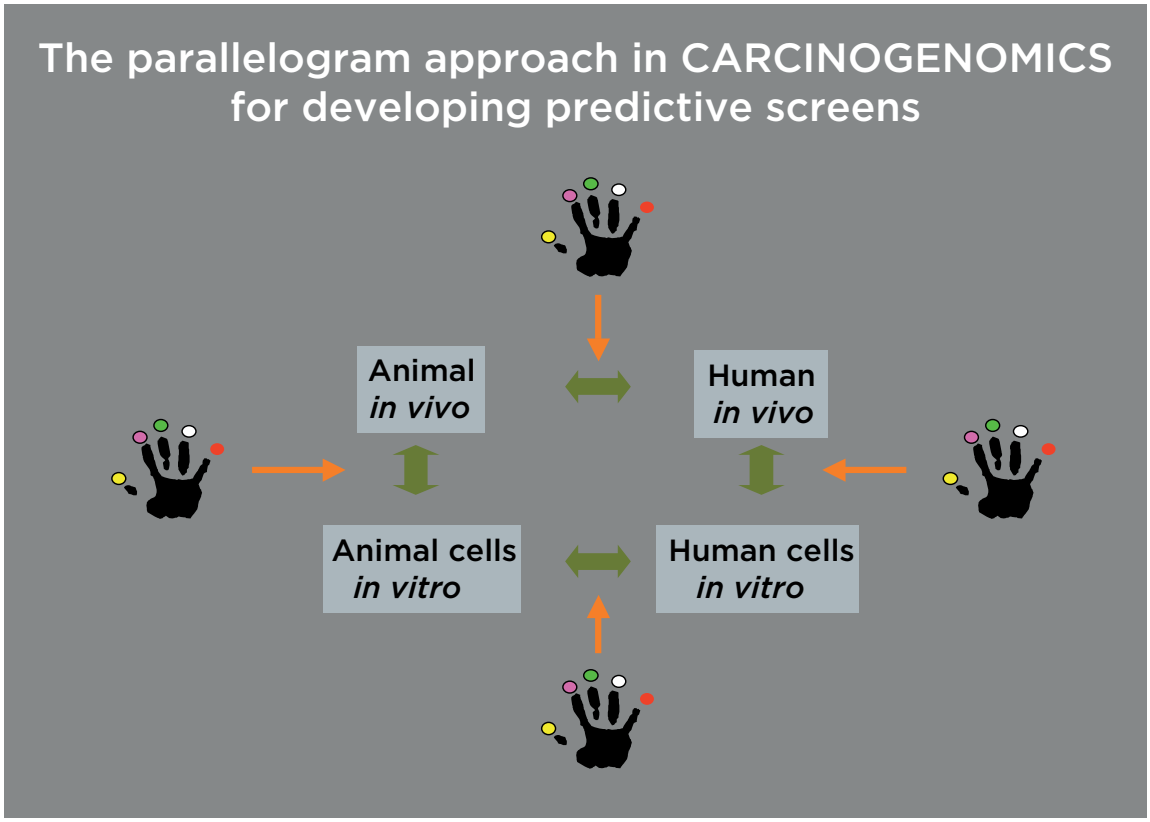
Aim

This project concedes to a crucial area within the LifeSciHealth Priority, namely "the Development of new *in vitro* tests to replace animal experimentation". With reference to the Three R Principle (Replace, Reduce, Refine) as highlighted in the LifeSciHealth Priority, the CARCINOGENOMICS project is directed towards replacing chronic rodent bioassays for assessing chemical genotoxicity and carcinogenicity.

For this purpose, CARCINOGENOMICS will produce innovative genomics-based *in vitro* screens for assessing carcinogenic properties of chemicals, with high throughput features which upon proper validation by ECVAM will bring technology applicable to REACH Combining pathway-associated gene expression with metabolic profiles generated *in vitro,* as is foreseen in the CARCINOGENOMICS represents a highly innovative approach possibly leading to *in silico* models that may be used to predict the carcinogenic potential of a compound *in vivo.*

With the aim to develop *in vitro* methods for testing the carcinogenic properties of compounds as an alternative to the chronic rodent bioassays for assessing chemical genotoxicity and carcinogenicity, the CARCINOGENOMICS project will address the following S&T objectives to:

- develop predictive mechanistic models based on transcriptome and metabonome profiling in rat and human primary cells from prioritized target organs, in order to discriminate genotoxic from non-genotoxic carcinogens;



- optimise cell systems into more robust cellular systems with an extended life span, stable phenotype, and xenobiotic metabolic competence;
- explore the suitability of embryonic stem cells as an alternative source of robust, human-derived cells for assessing target organ-specific carcinogenic actions;
- discern the biological pathways which in the predictive models are essential for class discrimination, and to test the pathway models for predicting carcinogenicity;
- build an *in silico* model for chemical carcinogenesis of the liver;
- describe inter-individual differences in the response to carcinogenic challenges;
- develop a specialized chip with high throughput features, in order to facilitate testing of large numbers of chemicals at high speed and low costs;
- pre-validate of the developed models according the ECVAM guidelines;
- investigate how the novel genomics-based *in vitro* tests for genotoxicity and carcinogenicity may fit within the EU regulatory and legal frameworks;
- establish a European public infrastructure giving an integrated view of the genomics data but also the associated phenotypical information;
- disseminate the outcome of the study to potential users.

Expected results

The project will deliver a battery of mechanism-based *in vitro* tests accounting for various modes of carcinogenic action. Based on 'omics' technologies, these tests will be designed to cover major target organs for carcinogenic action e.g. the liver, the lung, and the kidney.

Potential applications

In developing these toxicogenomics-based tests as alternatives to current chronic animal models for evaluating genotoxic and carcinogenic properties of chemicals, this project will significantly contribute to *better hazard and risk evaluation studies.* In order to study the impact of such knowledge including the availability of toxicogenomics-based predictive screens on *existing legislation and recent regulatory initiatives,* CARCINOGENOMICS features a separate sub-Workpackage on associated legal and regulatory issues.

The CARCINOGENOMICS consortium involves various *SMEs* in the areas of robust *in vitro* cellular systems, *genomics* analysis and bioinformatics, as well as with regard to high throughput technologies enabling *accelerated* and more efficient testing.

Project number
LSHB-CT-2006-037712

EC contribution
€ 10 440 000

Duration
60 months

Starting date
01/11/2006

Instrument
IP

Project website
www.carcinogenomics.eu/

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Keywords | Melanoma | genetics | naevi | sun exposure |

GenoMEL

Genetic and environmental determinants of melanoma: translation into behavioural change

Summary

GenoMEL, formerly known as the Melanoma Genetics Consortium, has focused on the identification of familial high-penetrance melanoma genes. To date, the consortium has been very successful in identifying susceptibility genes and developing joint data collection for gene/environment interaction studies. In order to continue its proactive role, GenoMEL is developing a multidisciplinary European platform with relevant input from international participants. This platform will also enable the investigation of attitudes to risk of melanoma in Europe, and translate that risk perception into behavioural change.

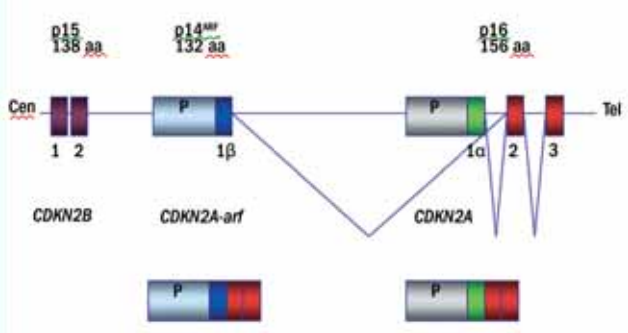
Problem

Melanoma is an important health issue within Europe because it continues to increase in incidence in many Member States and because it has a relatively flat-age incidence curve, so that the tumour is disproportionately frequent in young persons. Furthermore, in the new European Member States, there are concerns that as affluence increases incidence levels will rise precipitously if action is not taken to discourage risky behaviours in the sun. There are already, unfortunately, data suggesting that survival from melanoma is poorer in these European countries than in western European countries.

Aim

The objective of GenoMEL is to understand the genetic causes of melanoma and how the identified susceptibility genes interact with the environment, predominantly with sun exposure. The intent is then to use the information obtained to improve on the ranking of risk factors for melanoma and to understand the phenotypic markers of those susceptibility genes. These findings will then be converted into a web based tool, called a content management system (CMS), for use by the general public, in order to calculate individual risks of melanoma. The CMS will be assessed and correlated with reported behaviour in the sun. We will then 'close the loop' by designing materials for use primarily on the web but also as written materials to educate European people about the primary and secondary prevention of melanoma.

A GenoMEL researcher at work.



The CDKN2A locus – the first high penetrance melanoma susceptibility gene to be identified.

Project number
LSHC-CT-2005-018702

EC contribution
€ 10 452 723

Duration
60 months

Starting date
01/12/2005

Instrument
NoE

Project website
www.genomel.org

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Keywords | Virus | bacteria | HPV | HTLV | HCV | EBV | KSHV | HHV8 | helicobacter pylori |

INCA

The role of chronic infections in the development of cancer

Summary

Approximately 17% of the human cancer cases occurring worldwide are caused by infectious agents, in particular by viruses, bacteria and some parasites. Using a multidisciplinary approach, the INCA project will investigate the role of six of these infectious agents in the pathogenesis of infection-associated cancers.

Problem

To date, nine infectious agents have been recognised as human carcinogens by the International Agency for the Research on Cancer: Epstein-Barr virus (EBV), Kaposi sarcoma herpes virus (KSHV), Human papillomavirus (HPV), Human T-cell lymphotropic virus (HTLV-I), Hepatitis B virus (HBV), Hepatitis C virus (HCV), *Helicobacter pylori* (HP), *Schistosoma haemotobium* and liver flukes (*Opisthorchis viverrini, Clonorchis sinensis*). These nine infectious agents are responsible for about 17% of cancer cases worldwide, i.e. approximately 1.6 million newly diagnosed cases of cancer annually. In addition, more recent epidemiological evidence suggests that *Chlamydiae* could play a co-factor role in the development of cervical and lung cancer, and an involvement of enterohepatic *Helicobacter* in hepatobiliary tumours has been suggested. Moreover, infection-associated cancer is also of increasing importance in immunosuppressed individuals, i.e. transplant recipients and AIDS patients.

Aim

The INCA project will investigate the role of six of these infectious agents – EBV, KSHV/HHV8, HPV, HTLV-I, HCV, and HP – in the pathogenesis of infection-associated cancer. In addition, the co-factor role of enterohepatic HP will also be investigated.

The INCA Integrated Project aims towards a better understanding of the molecular and cellular circuits involved in the development of cancers caused by these infectious agents, of the mechanisms of long-term persistence of these infectious agents in apparently healthy hosts, and of genetic factors contributing to the development of these types of cancer.

Expected results

Based on this knowledge, INCA will develop and validate animal models to study chronic inflammation and cancer progression, and new diagnostic procedures for the identification of infected individuals likely to develop infection-associated malignancies. This will ultimately lead to the identification of new drugs and procedures to interfere with processes that are central to the development of infection-associated cancer. The results of this joint effort will contribute to the understanding of malignant transformation and provide new tools to address an urgent socio-economic and human need.

Potential applications

Diagnostics and therapy.

Project number
LSHC-CT-2005-018704

EC contribution
€ 12 400 000

Duration
48 months

Starting date
01/01/2006

Instrument
IP

Project website
www.inca-project.org

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Keywords | Breast | prostate | gene | association studies |

POLYGENE

Inherited risk of breast and prostate cancer

Summary

Studies of cancer families have identified high-penetrance cancer genes such as BRCA1 and BRCA2. However, although these genes have resulted in novel insights into cancer genes and pathways, it is clear that a large component of inherited cancer risk remains unaccounted for. It has been proposed that common low penetrance cancer susceptibility genes contribute significantly to the genetic predisposition of cancer in a polygenic model of inheritance. Association studies have been suggested as the method of choice for finding susceptibility alleles of high frequency but low penetrance. Here we propose to take advantage of accumulating genomic data and two European populations of different history and structure to determine the contribution of candidate cancer susceptibility genes to different clinical forms of breast and prostate cancer. We will use a population-based association study in Iceland and Holland to map the risk profiles associated with common polymorphic variants in and near candidate cancer susceptibility genes in breast and prostate cancer patients. We will also develop methods for statistical analysis of the resulting data. The proposed study has the potential to cast light on how genetic variants affect the risk of cancer initiation, and how it affects progression and response to treatment. Finally, the results may serve as a starting point for building models of genetic risk of these cancers.

Problem

Although several important genes have been shown to contribute to cancer susceptibility, multiple studies suggest that a major portion of such genes remain to be found. This is particularly true for prostate cancer. The major obstacles to finding those genes are the limited size of most studies and the inadequacy of the statistical methods available. Here we will address these problems by studying samples from two large populations of breast and prostate cancer patients and developing novel methods for the analysis of the resulting data.

Aim

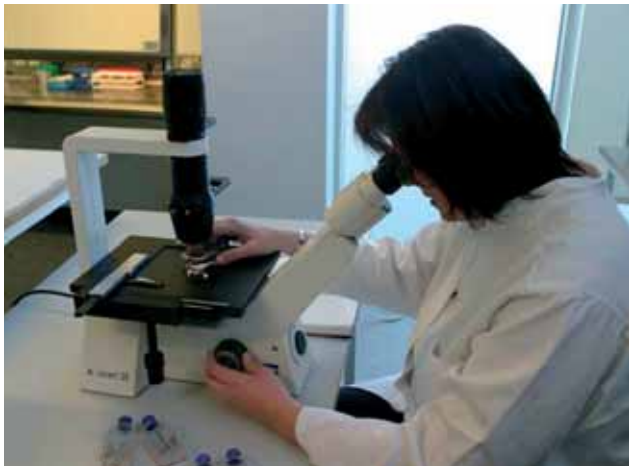
This project has two major aims: to determine the contribution of polymorphic variants in a large number of candidate genes to the risk of breast and prostate cancer, and to develop efficient statistical and computational methods for the analysis of genetic and association data.

Expected results

We expect to confirm or exclude the association of multiple candidate cancer genes with breast and prostate cancer in the Icelandic and Dutch populations. Also, the study may identify novel candidate cancer genes, which can translate into novel diagnostic markers for breast or prostate cancer and possible targets for therapy. In addition, we expect to develop novel statistical algorithms and software for analysis of genetic association data.

Potential applications

Potential applications include a commercial software package for the analysis of complex genetic data and novel cancer genes to be used as predictive markers for breast or prostate cancer risk, or for developing drugs.



An IGC researcher examines cells in tissue culture under the microscope.

Project number
LSHC-CT-2005-018827

EC contribution
€ 2 962 908

Duration
36 months

Starting date
01/11/2005

Instrument
STREP

Project website
www.polygene.eu

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Prevention

The fact that preventing the onset of a cancer is among the best treatment options is a well established and shared fundamental concept within the oncology community. Moreover it is widely accepted that the majority of cancers could be preventable.
The understanding of the extremely complex cancer aetiology is clearly the base for any prevention and treatment strategy to be effective. Regrettably, despite all the information available, still the rate of cure of tumours remains generally very low.
When prevention is considered it is not only a matter of deepening the scientific knowledge. This information has to be given a pragmatic value via a synergy with public health, education and support initiatives. The general population and the stakeholders in the capacity of taking such potentially effective actions have to be thoroughly and extensively educated.
Furthermore, when a cause is identified as potentially capable to have a strong correlation with the induction of a cancer, any action aimed at removing that cause should be carefully monitored to assess its real efficacy. This process has already brought in the past to the achievement of impressive and positive results connected with the measures taken in order to tackle the negative effects of smoking, alcohol and dietary intake.
Three EU funded projects foster the integration of the aetiology of cancer with preventive measures. These are: the Coordination Action (CA) 'EPIC' aimed at the production of a large mass of data potentially relevant for the identification of nutritional and environmental causes of cancer with the clear objective of establishing enhanced public health strategies for the prevention of cancer and other chronic diseases; the CA 'EUROCADET' aimed at underpinning and promote the implementation of European and national policies to prevent cancer and the Specific Targeted Project (STREP) 'MAMMI' aimed at enhancing early detection methodologies for breast cancer based on *beyond-state-of-the-art* Positron Emission Tomography (PET) imaging methodologies.

Alfredo Cesario

Keywords | Diet | lifestyle | physical activity | coronary heart disease (CHD) | stroke | chronic disease |

EPIC

European Prospective Investigation into Cancer, Chronic Diseases, Nutrition and Lifestyle

Problem

There are a series of complex relationships between a) the consumption of major foods and alcoholic beverages by different European populations, and b) the anthropometric characteristics and physical activity (PA) levels of different European populations and the causation/prevention of different cancers, coronary heart disease (CHD) and stroke.

Aim

The objective of this action is to reinforce and expand the collaboration between 27 European institutions so as to ensure that there is a major European resource containing:

- a very large database of 521 000 European subjects from ten European countries who provided detailed information on diet, lifestyle and health status between 1992 and 1999;
- a bio-repository of blood samples collected at baseline and stores in liquid nitrogen;
- follow-up data on over 28 000 cancer cases diagnosed after baseline, and over 15 500 deaths from all causes.

This will produce a large mass of data relevant for the identification of nutritional and environmental causes of cancer and other chronic diseases, and this knowledge will contribute to the development of effective public health strategies for the prevention of cancer, CHD and stroke.

This will also enhance the development of statistical methods for multicentre, Europe-wide studies on diet and chronic disease.

Expected results

New scientific knowledge will be gained on the roles that diet, obesity, physical activity, alcohol, tobacco and socioeconomic factors play in the risk of developing cancer, coronary heart disease and stroke in the ten European countries studied. This will include:

- a greater understanding of the complex relationships between these health outcomes, and diet and alcoholic beverage intake;
- updated results on the health-damaging effects of tobacco and the benefits of quitting tobacco;
- the identification of long-term disease risk prediction of biomarkers of diet, aiming to identify new biomarkers for the identification of subjects at increased cancer risk due to nutritional imbalances;
- methodological guidelines on quality/standardised methods for measuring diet and PA.

Scientific reports and papers will be published.

Potential applications

Recommendations for public health policies on strategies for the prevention of cancer, CHD and stroke in Europe, through the improvement of dietary habits and the promotion of a healthy lifestyle.

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€ 999 745

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Instrument
CA

Project website
www.epic.iarc.fr

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Keywords | Cancer incidence | prevention | risk factors | smoking | alcohol | overweight | fruit and vegetables | physical activity |

EUROCADET

Key determinants of the future incidence of cancer across Europe: impact of prevention

Summary

Up to 40% of Europeans will suffer from cancer at some time in their life and, in middle age, 40% of all deaths are due to this disease. Since up to 40% of cancers may also be preventable, primary prevention remains essential, as the European Cancer Code also emphasises. Entry-points for preventive interventions were identified based on known risk factors for cancer, partly overlapping with other chronic diseases. Yet, with the exception of hygienic and occupational measures and discouraging smoking, primary prevention was not very successful, especially in lower socio-economic status (SES) groups; avoidable exposure to risk factors demands more attention.

This project aims to underpin national and European policies to prevent cancer by providing estimates of the potential impact of interventions on determinants of cancer incidence on the future burden of cancer in Europe. Specifically, we aim to:

- estimate the prevalence and quantitative impact of major lifestyle (smoking, excessive alcohol use, fruit and vegetable consumption, overweight and physical activity) and socio-economic determinants on cancer incidence, concerning cancers of the oral cavity, larynx, lung, oesophagus, stomach, pancreas, colo-rectum, bladder, kidney, breast, endometrium and prostate, comprising 60% of the incidence;
- assess the potential to reduce exposure to these determinants by reviewing evidence of effectiveness of interventions and policies as well as barriers to implementation;
- estimate the future burden of cancer across Europe based on autonomous trends and various scenarios of implementation of effective interventions.

This coordination action will generate intensive interaction with national and international researchers, and policy-makers who will provide input to scenario development and reflect on its outcome so that ambitious policies can be rolled out. Regional workshops will serve to implement scenario development for prevention, based on the Prevent model developed at Erasmus MC in Rotterdam. A special web portal will be designed allowing for interactive communication among participants, archiving of relevant data and development of scenarios, and enabling Member States to adapt to their needs ('do-it-yourself') and circumstances, possibly also beyond the project.

Problem

Extensive research in the field of cancer aetiology and prevention has been performed in the last decades and is still going on. However, a systematic over view and integration of (in)effective strategies, their prerequisites, efficacy and possible impact is lacking. This project aims to integrate and synthesise the current knowledge of and experience with effective preventive activities, and project their expected effects on the future burden of cancer in Europe.

Aim

The aim is to underpin and promote implementation of European and national policies to prevent cancer by providing estimates of the potential impact that interventions directed at key determinants of the incidence of this disease may have on the future burden of cancer in the various parts of Europe up to 2040.

Expected impact

The impact of this project will be that a perspective for cancer prevention is shown, which makes maximal use of existing knowledge in such a way that policy-makers are persuaded to invest more in effective long-term prevention efforts. Furthermore, the project will help in formulating realistic targets at realistic terms (often over decades) to be reached by preventive measures designed to reduce the exposure to risk factors and/or the incidence of cancer, but also make recommendations for the further studies needed to improve primary prevention efforts to reduce the burden of cancer.

Potential applications

Benefiting from preventive actions directed at chronic diseases such as cancer, diabetes and cardio-vascular disease, this coordination action for cancer prevention prepares a solid basis for fur ther active evidence–based preventive policies that can affect many generations of Europeans born since the 1940s, but especially since the 1980s and 90s, by combining evidence with incentives to change unhealthy habits or not star t them, which is more relevant for the younger generations. European variation can provide an irresistibly strong example of the potential effects that changes in lifestyle can have. In this respect, the systematic attention for the role of socio-economic status (SES) is impor tant. The approach to estimate the long-term impact of prevention by means of scenario development opens the way for involving a broad array of stakeholders who are robbed of excuses not to act. The scenarios will be made available at a special web por tal, allowing the Member States and regions to adapt the input to their specific needs and circumstances, and creating an oppor tunity for interaction with policy-makers at European, national and international levels.

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SP23-CT-2005-006528

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Instrument
CA

Project web-site
www.eurocadet.org

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Keywords | PEMT | PET mammography | molecular imaging | breast cancer diagnosis | chemotherapy |

MAMMI

Mammography with molecular imaging

Summary

The proposed project focuses on the development of a PET prototype dedicated to the examination of breast cancer, using a gamma ray sensor based on an innovative design and the new generation of photo-detectors and scintillating crystals. The innovative features of the PEMT (Positron Emission MammoTomography) system we propose will imply a high resolution (pushed to the physical limit), higher sensitivity and lower cost. It includes integrated analogue and digital electronics through the design of an ASIC chip. The main application will be early breast cancer diagnosis and evaluation of chemotherapy response. New radio-tracer molecules will be searched for the detection and visualisation of the pharmacokinetics of breast tumours, more specific than glucose (FDG) for breast cancer, and based on human amino and fatty acids. Phase I Clinical trials will be performed with the new radio-tracers. A clinical multi-centric validation will be performed for the PEMT prototypes.

Problem

Breast cancer is the most common non-skin cancer and the leading cause of cancer death in women. The best condition for successful breast cancer treatment is early detection. Some studies indicate that early breast cancer detection has reduced the disease mortality by about 29%. The ability to define the extent of disease, to monitor response, and to predict tumour behaviour in patients with breast cancer are therefore important public health problems.

Conventional methods for breast cancer imaging like X-ray mammography, ultra-sound and Magnetic Resonance Imaging (MRI) produce morphologic and structural images, show lesions (like micro-calcifications), but not cancers. On the contrary, imaging methods based on Molecular Imaging show functional images, metabolism. This implies that they are much more sensitive and hence can be used to detect and locate malign tumours at an early stage. For instance, PET (Positron Emission Tomography) is a powerful tool for non-invasive molecular imaging diagnostic based on gamma ray (emitted by an isotope compound, previously administered to the patient) detection.

Aim

- Design and development of a dedicated low cost PET camera prototype for breast examination with an intrinsic resolution of less than 1 mm, high sensitivity, and tomographic 3D reconstruction.
- Study of new and more specific radio-pharmaceuticals for breast cancer detection and therapy monitoring (FLT, FAS, etc.). Perform phase I clinical trials of the radio-tracers.
- Clinical multi-centric validation of the new PEMT prototype.

Expected results

MAMMI proposes a new PET device specifically designed for breast cancer diagnosis and evaluation of therapy response. The dedicated breast cancer PET camera will improve the position resolution of current whole-body PET cameras (about 5 mm) and will push it to the physical limit (slightly below 1 mm).

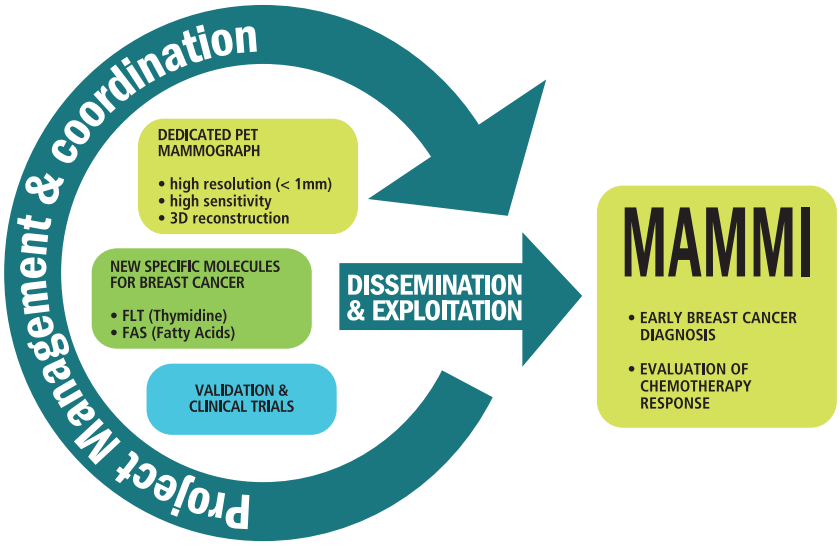
The new detector design will also have the ability to detect the depth of interaction of the gamma ray interactions within the crystal with a resolution better than 3 mm. This is an essential feature since it allows for an improvement of the final image resolution by almost eliminating the parallax error present in current PET detectors. This is essential in the case of breast examination since the detector cameras are placed close to the body, to increase the sensitivity.

The advantages of the new generation of photo-detectors (silicon photo-multipliers), such as their compactness, will be explored. The design of the electronics, including an ASIC, will allow an acquisition rate capability of the order of 1 MHz, with minimum dead time, to cope with the higher sensitivity.

Moreover MAMMI will develop and study more specific than FDG radio-tracers for breast cancer diagnostic and therapy monitoring, based on human amino acids (such as FLT) and fatty acids (such as FAS).

Potential applications

The main application will be early breast cancer diagnosis and evaluation of chemotherapy response. New radio-tracer molecules will be searched for the detection and visualisation of the pharmacokinetics of breast tumours, more specific than glucose (FDG) for breast cancer, and based on human amino and fatty acids.



Project number
LSHC-CT-2006-037555

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48 months

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01/01/2007

Instrument
STREP – SME

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Early Detection, Diagnosis and Prognosis

Cancer is one of the leading causes of death in Europe and the western world, second only to cardio-vascular diseases, a trend that is exacerbated by an aging population and increasing the economic burden of this disease. At present, diagnosis of cancer very often happens late in the course of the disease, when cancer cells have already invaded surrounding tissues and metastasised throughout the body, because current diagnostic methods are not sufficiently sensitive and specific. An early diagnosis of cancer would improve prognosis and treatment and could save thousands of lives a year with obvious advantages for public health care costs and quality of life.

Although advances in EU-wide breast cancer (mammography), prostate cancer (prostate-specific antigen testing) and cervical cancer screening (PAP smear and the likely introduction of PCR-based detection of human papilloma virus DNA) have provided important progress in the early detection and diagnosis of the disease, current diagnostic and prognostic biomarkers and methods still do not reach the sensitivity and specificity that is needed to reliably detect early-stage disease in the majority of cancers in for example non-invasive blood, urine, saliva, breath or stool assays. As a result, most therapeutic strategies are limited in their success or even doomed to failure.

The 25 projects in this section focus on the molecular characterisation of a series of cancers with the aim to translate this knowledge into novel early detection and diagnostic markers and tools, ranging from cancer (stem) cells in peripheral blood, lymph nodes and tumour tissues, breath-gas analysis, genetic tests to imaging probes and devices and endoscope technology.

Jan van de Loo

Keywords | Exhaled breath analysis | lung cancer | oesophageal cancer | medical diagnosis | therapeutic monitoring | gas chromatography | mass spectrometry | PTR-MS | SIFT-MS | laser spectrometry | ion mobility spectrometry |

BAMOD

Breath-Gas Analysis for Molecular-Oriented Detection of Minimal Diseases

Summary

Cancer is one of the leading causes of death in Europe and the western world. At present, diagnosis of cancer occurs late in the course of the disease since available diagnostic methods are not sufficiently sensitive and specific. An early diagnosis of cancer would improve prognosis and treatment, and could save thousands of lives a year.

There is strong evidence to suggest that particulate cancers can be detected by a molecular analysis of exhaled air. Breath analysis represents a new diagnostic technique that is without risk for the patient, even if repeated frequently, and can provide information beyond conventional analysis of blood and urine. Recent results suggest that detection of different kinds of cancer is possible by means of breath analysis in the very early stages of the disease.

This project is focused on the diagnosis of minimal disease and early stages of lung and oesophageal cancer. The analytical techniques will be gas chromatography with mass spectrometric detection (GC-MS), proton transfer reaction mass spectrometry (PTR-MS), selected ion flow tube mass spectrometry (SIFT-MS), laser spectrometry and ion mobility spectrometry (IMS).

In order to establish a reliable clinical method for the diagnosis of minimal residual cancer diseases, clinical expertise, basic research and technical development is necessary. The European consortium set up to pursue this research work involves specialists with skills in the fields of basic and clinical research, and analytical instrument development. Thus, the consortium has the expertise to investigate and screen exhaled breath for many molecular species, to identify specific cancer markers and the statistical tools to treat the data.

Problem

Cancer is one of the leading causes of death in the western world. More than 940 000 people died of lung cancer in Europe in the year 2000. These diseases have a tremendous impact on healthcare systems and economics. At present, the diagnosis of cancer often happens late in the course of the disease; early diagnosis would improve prognosis and treatment and could save thousands of lives.

Aim

The objectives of the project are:

- the identification of sensitive and specific molecular marker sets in human breath for the detection of early cancer stages;
- the development of reliable analytical methods to detect these markers in the clinical environment;
- the production of easy-to-use and non-expensive equipment to facilitate breath analysis as a novel cancer screening tool.

The proposal is centred on five studies: *in vivo* lung cancer and oesophageal cancer studies, a study of cancer cell lines *in vitro,* a study of immune-system related cells and a study of bacterial cell lines.

The SMEs in our consortium will develop analytical methodology for subsequent use in clinical applications.

Expected results

The major objective is the establishment of a non-invasive, breathbased test for early detection of lung and oesophageal cancer. The development of sensitive detection technology, a database of molecular markers related to cancer, and the development of specific sensors for such markers is anticipated.

Potential applications

The developed breath-based tests for the detection of lung and oesophageal cancer should be introduced to assist clinical diagnosis and therapeutic monitoring.

Detection of lung and oesophageal cancer based on exhaled breath.

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LSHC-CT-2005-019031

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Instrument
STREP

Project website
eu-proposal.voc-research.at

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Keywords | Molecular tumour imaging | cancer therapy | PET-based treatment planning | PET-CT simulation | apoptosis | tumour hypoxia | aptamers | PET-CT-RT | diagnostic treatment unit |

BioCare

Molecular Imaging for Biologically Optimised Cancer Therapy

Summary

Early tumour detection and response monitoring require maximum sensitivity and specificity of the imaging method. This project focuses on the clinical evaluation and development of new, more specific molecular tracers for the early detection of tumour cells. A large number of new and potentially more specific tracers than fluorodeoxy-glucose (FDG) will be tested, including amino acid analogues, small tumour-binding peptides, aptamers, peptides binding to mutant p53 proteins and nanoparticles. The more tumour specific the tracer, the more accurately it will be possible to image the true tumour cell density and, more importantly, the true response of the tumour to therapy.

There is also a need to consolidate experience in the use of recently developed molecular tracers to assess radiotherapy and chemotherapy response in order to improve on state-of-the-art treatments. To maximise the sensitivity and tumour image quality, a high-resolution, wide field-of-view, ultra-sensitive fully integrated PET-CT camera, capable of imaging half the human body in a few minutes, will be designed. Furthermore new adaptive therapy planning and biological optimisation codes and a dedicated PET-CT detector for incorporation in treatment units will be designed in close corporation with university researchers and SMEs. This will allow an efficient clinical integration and high patient throughput. The associated increase in accuracy of tumour imaging and the three-dimensional *in vivo* tumour responsiveness data will hopefully allow the clinical introduction of accurate biologically based adaptive treatment optimisation methods.

Problem

Cancer imaging is at the dawn of a third revolution of accurate tumour diagnostics. During the 1970s and early 1980s, computed tomography (CT) with diagnostic X-rays made a revolution in accurate delineation of normal tissue anatomy as well as gross tumour growth. In the mid 1980s and 1990s, magnetic resonance imaging and spectroscopy (1.2) allowed even more accurate differential diagnostics of soft tissue malignancies with the possibility of distinguishing between tumour tissues, oedema and normal tissues. The integration of positron emission and X-ray computed tomography in one unit and MRSI – MR spectroscopic imaging – is bringing a third diagnostic revolution to tumour imaging. By combining these two imaging modalities, an unprecedented accuracy in the delineation of the tumour on a background of normal tissue anatomy is achieved.

Obviously, fluorodeoxyglucose (FDG) is not tumour-specific, as all regions with an increased metabolic rate will show an elevated uptake. However, in the new era of molecular imaging it is likely to be followed by more specific tumour markers, allowing an even more accurate imaging of the tumour clonogen density. Methionine and other amino acids are already available as tracers and, although they may be better than FDG, they may still not be sufficiently specific, since they are incorporated in all tissues that are being renewed. For some tumours, there are more specific markers such as ^{11}C-Choline, and FHBC or FDHT (fluorodihydrotestosterone) for imaging androgen receptors in prostate cancer. Vasculature could be visualisable by known tracers such as ammonia ($^{11}CH_3$) or water ($H_2\ ^{15}O$).

Aim

Molecular imaging of radiation-induced alteration of tumour cell proliferation and functional receptor expression. In recent years, radiotracer-based molecular imaging with positron emission tomography in oncology has evolved as a valuable tool for staging of disease and evaluation of therapy response. This success is mainly based on the application of the glucose analogue 18Fluorodeoxyglucose, which traces tumour tissue by the fact that most tumours exhibit enhanced glucose consumption. But the tumour microenvironment is not depending only on glucose metabolism. Perfusion, hypoxia, amino acid uptake and receptor status are important parameters which have high impact on the treatment success. Additionally to 'the classics', FDG and methionine, new PET-tracers to monitor these parameters are under development. With the advent of high-resolution animal PET scanners there is now the opportunity to investigate *in vivo* the tumour microenvironment of transplanted tumours in small animals under therapy conditions, especially for radiation therapy – for example the knowledge on the course of oxic or hypoxic conditions has the potential to develop strategies to overcome treatment failure due to hypoxia-related radiation resistance. PET offers the opportunity to investigate the radiation response of tumours longitudinal during the treatment time, to evaluate the predictive strength of different parameters or their combination, and to test the efficacy of newly developed tracers in comparison to 'standard tracers'. The functional PET data will be supplemented by tumour histology, immunohisto-chemistry and autoradiography to complement the tumour-pathophysiologic data.

In the future we thus need improved tracers to the image tumour spread before treatment. This will enable accurate delineation of the clinical target volume based on visualised uptake by the tumour, for example along well-known pathways of microscopic lymphatic invasion.

Aptamers. Molecular imaging, the science that combines non-invasive *in vivo* imaging and molecular biology, has begun to use labelled oligonucleotides as radiotracers. The aptamers, single-stranded oligonucleotides have a complex three-dimensional structure and can interact with suitably conformed proteins with an affinity and specificity comparable to that of receptor–ligand binding. Systematic evolution of ligands by exponential enrichment (SELEX) is an empirical technique for selecting oligonucleotides that will bind to a given target, using a repetitive process of selective binding and amplification by polymerase chain reaction. Like phage display, SELEX offers the potential of rapidly designing radiolabelled ligands for almost any target. The labelling of single-stranded oligonucleotides with a positron or single-photon emitter can result in valuable radiopharmaceuticals with promising applications for:

- imaging of specific mRNAs, i.e. visualisation of the expression of specific genes *in vivo*;
- monitoring of antisense chemotherapy, i.e. measuring the efficiency of efforts to block the expression of specific genes;
- gene radiotherapy, i.e. the targeting of radiation damage to specific DNA sequences in order to destroy tumours;
- imaging of protein targets by the use of aptamer oligonucleotides, i.e. oligonucleotide ligands obtained by *in vitro* evolution of selection-amplification steps, or selected for their interaction with nucleic acid-binding proteins;
- pre-targeting strategies based on the specificity of complementary sequence hybridisation. Nevertheless, oligonucleotides are intrinsically poor pharmaceuticals because of their large size, low stability, poor membrane passage and a number of undesirable and sometimes unpredictable side effects. As an alternative to the inherently unstable phosphodiester DNAs, chemically modified oligonucleotides, such as phosphorothioate, methylphosphonate and peptide nucleic acid oligomers, have been developed, and some are in clinical trials for the chemotherapy of several types of tumours. Imaging techniques could be useful in the development of such therapies. In addition, the potential of targeting virtually any disease or physiological process, by changing only the sequence of the oligomer, could provide a means of identifying serious diseases in a very early stage, and be a highly specific modality to diagnose and differentiate various cancers. This has stimulated efforts to develop such radiopharmaceuticals in many laboratories, and encouraging results have been reported using technetium-99m, indium-111, carbon-11, fluorine-18, bromine-76 and iodine-125 labelled oligonucleotides.

The overall goals are two-fold namely:

- to improve and speed up the implementation of PET-CT imaging in cancer management;
- to develop new European intellectual property to improve tumour imaging by more specific tumour tracers. They will result in considerably increased resolution, sensitivity and specificity in tumour detection.

Our research project is subdivided into four major activities addressed through nine work packages.

Activity	Work packages
PET-Camera Developments	1
Development of New Tracers	2, 3, 4, 5, 8
Experimental and Clinical Validation	3, 6, 7
Implementation in Medical Oncology	6, 7, 9

Expected results

WP1 Proof of principle of 1 mm resolution PET and fully integrated PET-CT detection for diagnostic and therapeutic applications.

WP2 Development of assay allowing distinction between apoptotic versus necrotic cell kill. Study of possibilities to image the mutant p53 protein *in vivo*.

WP3 Development and workshop on human tumour model assessment by small animal PET.

WP4 Development of aptamers for tumour-associated target structures.

WP5 Development and clinical testing of new hypoxic tumour markers.

WP6 Development and validation of high quality FDG, FLT and FRT methodologies for PET-CT imaging in European centres.

WP7 Development of accurate methods for PET-CT-based treatment simulation and therapy verification for biologically optimised intensity modulated radiation therapy.

WP8 Development, testing and pharmacogenetic characterisation of radiolabelled angiogenesis inhibitors.

WP9 Development of biologically optimised predictive assay and adaptive treatment planning techniques based on PET-CT tumour and dose delivery imaging.

Potential applications

Beside the significant improvement in sensitivity and specificity for early tumour detection and response monitoring with the new tracers, detection systems and algorithms developed in the project, a large number of SMEs will be involved in developing products of general interest to the entire cancer community. The SMEs are an integral part in the project in making the new tools available, not only for Europe but also for the world market. The close integration between clinical and research activities at numerous university hospitals with the SMEs will form new centres of excellence where European SMEs will benefit from close clinical and research collaboration at the same time as new products will be developed to the benefit of cancer patients.

These centres of excellence will integrate the five cornerstones of European societies:

- basic and clinical research;
- innovation and advanced product development;
- clinical practice and experience;
- entrepreneurs or SMEs;
- the marketplace in medical applications represented by hospital care systems. Sometimes it is relevant to include venture- and research-capital investors as a sixth entry in this listing. The centres of excellence formed by the collaboration in the present project will be a unique engine for European development in cancer care for the new millennium.

Project number
LSHC-CT-2004-505785

EC contribution
€ 6 000 000

Duration
55 months

Starting date
01/03/2004

Instrument
IP

Project website
www.biocare-eu.com

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Keywords | Monoclonal antibodies | bispecific | bifunctional | nanoparticles | genetic engineering | leukaemia and lymphoma | cancer therapy |

BMC
Bispecific Monoclonal Antibody Technology Concept

Summary

Monoclonal antibodies (mAbs) represent a new form of protein-based drug having demonstrated a significant impact on the treatment of several types of cancers. Their specificity towards cell surface receptors makes them able to target and destroy tumour cells. However, much progress is still necessary to understand the mechanism of the binding and activity of antibodies in order to improve their targeting capabilities and their efficiency. To reach these objectives, the BMC project will:

- develop a recombinant bispecific mAb with tetrameric binding sites, directed against two different antigens expressed on the same target tumour cell;
- develop new bispecific or bifunctional molecules with the property of cross-linking two different receptors on the surface of the cell;
- modify the carbohydrate moiety of bispecific antibodies and the tumour targeting of the complement regulator molecule, properdin, to trigger the activation of the complement enzymatic cascade at the tumour site.

The recombinant molecules are directed against a selected target antigen for mAb therapy, CD5, as well as a B-cell marker to be selected, in order to treat a specific type of leukaemia, the B-CLL. However, the described innovative cancer immunotherapy strategy will also be extended to the treatment of many other types of cancers, especially all carcinomas.

The consortium is made up of nine partners:

- six RTDs specialising in genetic engineering (CNRS), innovative molecule design (UNIL), antibody vectorisation with nanoparticles (HUJI), CDC activity improvement and cell line and animal model development (UBO), mechanisms of therapeutic antibodies on patients' cells (OORRBG), toxicology studies and standardisation (ITEM);
- two biotechnology SMEs specialising in therapeutic antibody development (MAT) and antibodies *in vitro* production (MABGENE);
- one company dedicated to the project management – ALMA.

Problem

Monoclonal antibodies given as a single modality treatment induce tumour remissions in less than 50 % of patients with well-selected type of cancer; complete tumour remissions are scarce. Thus, while the rapid introduction of mAbs for cancer therapy is very encouraging in favour of the use of this type of biological molecule, much progress is still necessary to understand the mechanism of the action of therapeutic mAbs in order to make them more specific and efficient in a broader range of cancer types. Indeed, it is a paradox that despite the great success of some well-selected mAbs in the treatment of some cancer types, the principal mechanism by which mAbs are inducing the destruction of cancer cells has not yet been completely elucidated. Furthermore, the reasons why some patients respond to mAbs therapy, while others with almost the same tumour do not, is not yet understood. The possible causes for a poor response to mAbs therapy include a low density of target antigen on the surface of tumour cells, which limits the activity of complement mediated cytotoxicity (CDC), and of antibody dependent cell-mediated immunity (ADCC), a low sensitivity of tumour cells to an apoptosis signal or a poor accessibility of the injected mAbs to the tumour cells.

Aim

The global aim of the project is to improve the monoclonal antibody therapy with special emphasis on B-Chronic Lymphocytic Leukaemia and Mantle zone B-cell lymphoma, which will be achieved by:

- a link between targeting and activity: increase of understanding of apoptosis signalling;
- exploitation of the complement activity on tumoural cells as it is known to function on bacteria, overcoming the known inhibitory molecules present in eukaryotic cells;
- development of novel approaches to optimise the targeting and destruction of tumoural cells by:
- engineering new constructs of recombinant bispecific or bifunctional antibodies reacting with two different antigens on the same tumour cells;
- developing new strategies for the induction of complement-dependant cytotoxicity (CDC), either through modifications of the glycosylation of bispecific monoclonal antibodies, or by genetically fusing properdin to recombinant monoclonal antibodies;
- chemical conjugation of antibodies of different specificities on emulsion nanoparticles;
- evaluation and validation of the novel tumour targeting strategies proposed in the BMC project on tumour cells from patients with $CD5^+$ B-cell lymphoproliferative diseases, as well as in an experimental model of SCID mice grafted with $CD5^+$ B-cell lines.

Project number
LSHB-CT-2005-518185

EC contribution
€ 2 450 000

Duration
36 months

Starting date
01/11/2005

Instrument
STREP

Expected results

Optimise the benefit/risk ratio in B CD5⁺ B-cell leukaemias and lymphomas.

Potential applications

This could be applied to other types of cancer.

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Keywords | Metalloproteinase | protease | metastasis | diagnostics | tumour imaging |

CANCERDEGRADOME

Extracellular proteases and the cancer degradome: innovative diagnostic markers, therapeutic targets and tumour imaging agents

Summary

Extracellular proteases have complex roles with distinct functions at different stages of tumour development and progression, and may have conflicting effects on malignancy. The complete repertoire of extracellular proteases through which cells regulate their local environment is termed the Degradome. Extracellular proteases remain an attractive target for intervention against cancer and we propose to transfer recent insights into their function to pre-clinical and clinical settings.

Problem

The critical defining feature of a malignant tumour is the presence of cells that have broken through tissue boundaries and penetrated into surrounding normal tissues. It has long been recognised that cellular invasion of basement membranes and connective tissue stroma involves the actions of diverse extracellular proteases from multiple enzymatic classes, including the metalloproteinases (MPs) and the serine, threonine, thiol and aspartic proteases, which can be produced either by cancer cells themselves or by neighbouring host cells. These cellular proteases participate also in the formation of new blood vessels that support the burgeoning energy demands of a rapidly growing tumour, and in the ability of cancer cells to metastasize to distant organs. They constitute the Degradome – the complete repertoire of proteases that cells and tissues coordinatively regulate in order to modulate their local environment.

We now understand that pericellular proteolysis is important in the regulation of:

- growth factor activation, bioavailability and receptor signalling;
- cell adhesion and motility;
- apoptosis and survival mechanisms;
- angiogenesis;
- specification of cellular identity;
- inflammatory responses and immune surveillance.

In the battle against cancer, the Degradome is important in three principal areas.

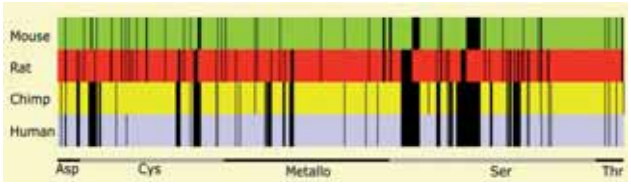
- Cellular proteases and their inhibitors are components of the molecular machinery of malignancy, and thus are attractive as therapeutic targets.
- Degradome genes are valuable as prognostic and diagnostic markers of disease that can improve the accuracy of conventional clinical and histopathological assessment.
- Cellular proteases are target molecules for improving tumour detection and imaging.

The goals in molecular diagnostics are to develop molecular profiling technologies and markers of disease status that are broadly applicable to the selection of patients for therapy, or to screening of disease-free individuals who may benefit from prophylactic interventions.

Aim

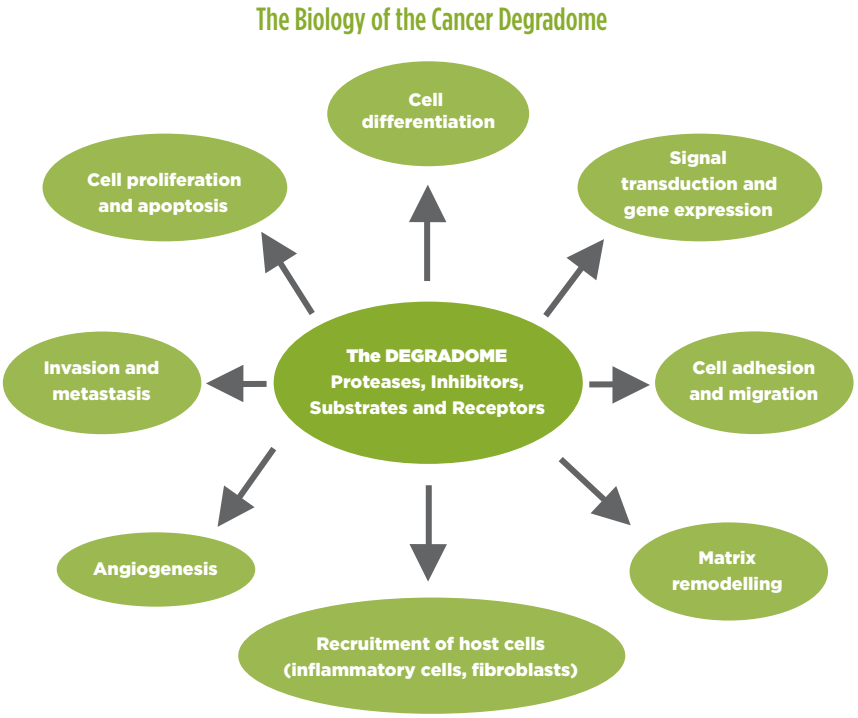
The aim of this project is to define new molecular targets for drug design and to develop novel specific interventions that are based on thorough knowledge of the pathophysiological roles of target proteases and related molecules, and to understand how and when to use them. The identification of new molecular diagnostic and prognostic indicators of patient risk, together with new ways to enhance visualisation of tumours in the clinic, will improve health care delivery based on an individualised, patient-oriented approach to cancer therapy.

Overview of human, chimpanzee, rat and mouse degradomes



The figure represents the complete set of protease and protease homologue genes from the indicated species. Catalytic classes are indicated at the bottom.

X.S. Puente, L.M. Sánchez, A. Gutiérrez-Fernández, G. Velasco and C. López-Otín, *A genomic view of the complexity of mammalian proteolytic system.* Biochem. Soc. Trans. (2005) 33, (331–334).



Targets of molecular therapeutics can be found in different aspects of malignant transformation.

Expected results

- The determination of Degradome gene expression patterns in human tumour cell lines and mouse models.
- A detailed analysis of Degradome gene function using tumour prone mouse models.
- The analysis of protease inhibitor function in combination with other therapies.
- Elucidation of the interplay between proteases and other key molecules of intracellular and intercellular signalling.
- Determination of the regulatory factors that control protease gene expression in tumours and in the tumour-host dialogue.
- Characterisation of the cellular expression of Degradome genes for breast and prostate cancer.
- Development of active site-directed inhibitors of metalloproteinases.
- Development of ligands able to prevent the formation of protease-substrate, protease-inhibitor, protease-receptor complexes.
- Production of radiotracers for protease ligands for *in vivo* imaging, with transfer to clinical paradigms.

Potential applications

Several major pharmaceutical companies have been involved in the development of synthetic protease inhibitors for cancer therapy over the past decade. However, the vast majority of trials have shown these first generation compounds to have limited effects. What is now clear is that the biological activities of extracellular proteases, and their roles in normal and diseased tissues, are much more complex than was originally envisioned. The original notion of proteases solely as mediators of pathological tissue destruction is an oversimplification: in fact, some proteases have functions that inhibit tumour development and progression, and moreover, their natural inhibitors (TIMPs, PAIs, etc) can in some instances enhance tumourigenesis. The identification of protease targets for the design of novel and specific interventions will offer improvements for health care delivery and patient management. The knowledge obtained in this project can also be used to identify cancer susceptibility in otherwise healthy individuals.

Project number
LSHC-CT-2003-503297

EC contribution
€ 10 400 000

Duration
48 months

Starting date
01/01/2004

Instrument
IP

Project website
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Keywords | Biomarkers | colon cancer | breast cancer | follow-up diagnostics | screening | transcriptomics | genomics | proteomics | metabolomics | data mining |

COBRED

Colon and Breast cancer Diagnostics

Summary

COBRED aims at the discovery of colon and breast cancer biomarkers for patient follow-up (monitoring markers). COBRED will exploit the high-throughput analysis capacity of transcriptomics, proteomics and metabolomics technologies in an integrated systems biology approach and the expertise of biotech SMEs and academic partners to discover biomarker candidates. Two clinical institutes renowned for their expertise in colon and breast cancer will participate in the study with the design and execution of a prospective clinical collection and will carry out the biological and clinical validation of the efficiency of the identified biomarkers. After 3 years COBRED will deliver a set of biomarker candidates verified in preclinical studies, ready for large scale clinical validation and further development for commercialization by the respective SME partners. Furthermore COBRED will have demonstrated the potential to explore consolidated data resulting from different high-throughput technologies and clinical profiles with advanced data mining technologies for enhanced biomarker discovery.

Although within the project scope COBRED focuses on biomarkers for follow-up diagnostics, it has the potential to evolve to an early cancer detection & screening tool.

Problem

An apparent paradox of current cancer epidemiology is that while new therapies and diagnostics improve survival rates in common cancers, e.g. colon and breast cancer, the incidence rates are also increasing, thus the net effect is negative.

Colorectal cancer (CRC) is the third commonest cancer type worldwide; in the year 2000 the global incidence was about 1 million, close to 10% of all cancers, and it resulted in about 0.5 million deaths, equalling of about 8% of all cancer mortality. Breast cancer (BC) is the most common cancer in Western women. In these patients, it is not the primary tumour, but its distant metastases that are the main cause of mortality. The yearly incidence rate is over 0.5 million (630 000 new breast cancer cases) that results in about 0.2 million deaths. Recently, the rates of metastasis and mortality in BC patients have decreased as a result of early diagnosis by mammographic screening and the implementation of systemic adjuvant therapy similarly to CRC. There is ample, but 'only' circumstantial evidence that derives from survival data of patients with early stages of cancer, suggesting that earlier diagnosis would allow 10-20% survival rates improvement. In fact, the potential benefits of early CRC and BC diagnosis are so high that a wide range of community and governmental efforts have been implemented for population wide screening.

Biomarkers are substances found in the blood, other body fluids (e.g. urine) or tissues that alone or in combination may signal the presence of cancer or the risk for cancer. Diagnostics based on biomarkers have the potential to significantly improve current cancer diagnostic means, providing a higher sensitivity (i.e. much smaller tumours can be detected), easier and faster and at a much lower cost. Biomarker discovery and validation, similarly to drug discovery and validation, is a long process with high rate (60-80%) of attrition of candidate biomarkers along the major steps of qualification that ultimately ends in the approval by the Food and Drug Administration (FDA) in the US and the European Agency for the Evaluation of Medicinal Products (EMEA) in the EU. Often, seemingly good candidates that have been identified and found valuable in one study do not show the expected predictive values in the second study. In fact, the number of new diagnostics approved per year is decreasing in sharp contrast to the intensifying biomarker discovery efforts. Thus, despite having the highest potential value in numbers, COBRED choose not to pursue the discovery of screening markers because of economic and logistic impracticalities of a large scale screening-marker validation in BC and CRC. Instead, we focus on the second largest clinical need, the improvement of patient follow up, by the discovery of monitoring markers, which are expected to report relapse, metastasis and minimal residual disease at earlier stages, which are more amenable to surgical and chemotherapy treatment, and more likely to improve cancer patient survival.

Aim

The specific RTD objectives are to:

- design a clinical protocol for prospective clinical BC and CRC collections that fit the needs of the 3 high-throughput screening technologies used: transcriptomics, proteomics and metabolomics;
- identify biomarker candidates (metabolites, proteins, PBL derived mRNAs) capable to detect and assess the status of minimal residual disease, metastases and recurrence after surgery and chemotherapy;
- develop a centralized database to integrate the data generated by the 3 technology platforms with the anatomo-clinical information of the clinical collections;
- discover biomarkers with better specificity and sensitivity using across-platform advanced data-mining techniques on the combined data from the consolidated database;
- validate the biological relevance and diagnostic potential of the identified biomarkers by testing their specificity on tissue arrays and in relevant preclinical models.

Project number
LSHB-CT-2007-037730

EC contribution
€ 2 985 102

Duration
36 months

Starting date
01/03/2007

Instrument
STREP

Project website
www.cobred.eu

Expected results

Specific project results will include:

- sets of biomarkers (gene signatures, proteins, metabolites or a combination of these) that will be considered clinically relevant for early diagnosis of primary BC and CRC and relapses;
- central repository system hosting the results from the technological platforms and the relevant clinical data;
- prospective clinical collection of BC and CRC;
- clinical validation for the diagnostic potential of subsets of the identified biomarkers in comparison to existing biomarkers and to currently available imaging techniques;
- preclinical models for the biomarker evaluation and biological studies.

Potential applications

Diagnostic kit for the detection of cancer recurrence and metastasis, with the longer term goal to develop early cancer detection tests amenable for population screening.

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Keywords | Clinical diagnosis | cancer | infrared spectroscopy | infrared microscopy | infrared imaging | synchrotron radiation |

DASIM

Diagnostic Applications of Synchrotron Infrared Microspectroscopy

Project number
LSSB-CT-2005-005326

EC contribution
€ 280 000

Duration
36 months

Starting date
01/07/2005

Instrument
SSA

Project website
www.dasim.com

Summary

DASIM is a Specific Support Action to coordinate research effort of all Europe's synchrotron light sources in the field of infrared microspectroscopy of pathological samples as an aid to clinical diagnosis.

Problem

Diagnosis of disease is the basis for all clinical medicine. The primary requirement is reliability of diagnosis in order to ensure that therapies are appropriate and successful. However, the modern requirements of clinicians from diagnostic services go beyond a simple 'yes' or 'no' to the presence of a particular indication. Successful therapy requires information on disease subtype classification, assessment of the disease stage and extent such as the grading of tumours, as well as the monitoring of disease progress and therapeutic success. The speed of pathological analysis can also be amongst the requirements arising as a result of a time-limited therapeutic window beyond which therapy may be less or no longer effective. Such constraints are particularly apparent in the treatment of cancer and infectious diseases. Post-mortem diagnosis is also an aspect to be included, since there remain some diseases that can only be unequivocally diagnosed post mortem, and in these cases the retrospective diagnosis plays a central role in improving therapies through the accumulation of clinical experience.

Aim

In the last ten years there has been considerable progress in the application of infrared microspectroscopy to the analysis of human tissues in the context of disease diagnosis, and it has been convincingly demonstrated in many studies that infrared spectroscopy has the potential to contribute significantly to this field. The aim of DASIM is to coordinate this research effort by networking the existing centres of excellence across Europe, by providing a forum for the necessary multidisciplinary exchange of expertise between clinicians, spectroscopists, biologists and physicists on the European scale, and by facilitating access to synchrotron facilities for scientists and clinicians in countries that do not have their own synchrotron facility.

Expected results

- Significant acceleration of the rate of progress in the field by coordinating the research effort.
- Dissemination of knowledge through meetings, courses, website and publications, informing clinicians in particular.
- Reliable assessment of the potential of this technique as a guide for future EU science funding policy.

Potential applications

Clinical diagnosis, particularly typing, staging and grading of tumours.

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Keywords | Tumour cell dissemination | micrometastases | minimal disease | biobanking | genomic profiling | microarray analysis | circulating nucleic acids | bioinformatical synopsis |

DISMAL

Molecular Signatures as Diagnostic and Therapeutic Targets for Disseminated Epithelial Malignancies

Summary

Disseminated tumour cells (DTC) occur at very low numbers in the blood and particularly in the bone marrow, and can be detected using sensitive immunostaining and PCR methods. However, the sensitivity and specificity of this approach need to be improved. Combining the expertise of 11 academic partners with long-term expertise in micrometastasis research, the DISMAL project will establish an improved platform for DTC detection with an increased sensitivity and, in particular, with a greatly improved specificity. Besides DTC detection, the combination with analysis of circulating tumour DNA and RNA as well as the expression profiling of tumours are being explored to improve the assessment of minimal disease. We will focus on epithelial tumours, as they are the most common types of solid tumours in the EU, investigating the carcinoma types that display different modes of metastatic spread. Dissemination via the blood circulation will be analysed using bone marrow as this is the most important indicator organ epithelial tumour cells home in on. Using genomic-based approaches, novel diagnostic target molecules will be identified on these cells and validated in functional models. We will complement immunocytochemical DTC detection by additional genotypic and phenotypic markers relevant for metastatic progression. To further increase diagnostic precision, we will analyse whether this improved platform can be combined with the analysis of tumour characteristics that were revealed by microarray profiling, and with evaluation of circulating tumour-associated DNA or RNA. Besides the primary focus on improvement of DTC-based diagnostic platforms, it is important to realise that these cells are the target cells for any kind of adjuvant systemic therapy, including chemotherapy and targeted biological therapies. In innovative DTC models, the efficacy of DTC treatment will therefore be analysed and potential improvements studied. The translation of scientific knowledge into commercial products will be ensured by three SMEs with unique technological capabilities.

Problem

Investigations during the last decades have shown that the metastatic cascade is a complex pathobiological process and highly dependent on the type of tumour. Some tumours, such as breast cancers, have a proclivity for parallel dissemination to the haematogenous and lymphatic compartment, starting in the earliest phases of tumour development. In other tumour types, such as in head and neck cancer, this pattern is very different and haematogeneous dissemination appears to result from metastases in the lymphatic compartment. For these reasons we selected three tumour types: one as an extreme example of parallel, independent dissemination (breast cancer), one as an extreme example of sequential dissemination (head and neck cancer), and one intermediate type (colorectal cancer).

Aim

The main objective of the DISMAL-project is to improve the specificity and sensitivity of current platforms for DTC detection in patients with epithelial tumours, the predominant form of cancer in Europe, whilst also identifying novel markers at the DNA, RNA or protein level that allows a more precise detection of DTC with a high risk for metastatic progression.

The programme will focus on markers associated with haematogenous dissemination (using bone marrow as the most well defined indicator organ) because these markers have the potential to become novel targets, not only for diagnostic purposes but also for therapeutic interventions. The markers functionally associated with metastatic progression of DTC are likely to be promising targets for therapy. These specific markers could be further developed as therapeutic targets in collaboration with SMEs and larger pharmaceutical industries.

With regard to cancer therapy, two key issues will be addressed. First, it will be evaluated whether it is possible to eradicate DTC by an immunotherapeutic approach, optimised for success in a mouse model. Secondly, we will investigate whether DTC are susceptible to current systemic therapies (for example chemotherapy) and develop novel approaches for their specific eradication. Current adjuvant chemo- or radiation therapy aims at hitting the most overt property of tumour cells their unrestricted potential to proliferate. According to our current knowledge, DTC in the bone marrow are non- or slowly proliferating.

Project number
LSHC-CT-2005-018911

EC contribution
€ 4 200 000

Duration
36 months

Starting date
01/11/2005

Instrument
STREP

Project website
www.dkfz.de/dismal

Expected results

Primarily, the result of DISMAL will lead to improved disease staging and when implemented in clinical practice to personalised medicine. As a long-term goal, reaching beyond the duration of this proposal, the newly discovered diagnostic markers will be further evaluated for their suitability as targets for therapeutic intervention, specifically aimed to eradicate minimal residual disease (MRD) in patients with solid tumours. DISMAL will provide:

- knowledge about the biology of the metastatic process, particularly genes that determine early dissemination, homing and survival of epithelial tumour cells at different sites;
- identification of relevant genes and signalling pathways associated with tumour cell dissemination via the blood vessels to distant organs (bone marrow);
- improved estimation of prognosis and need for therapy of cancer patients with minimal disease through the development of a novel diagnostic platform for DTC detection which includes the information on the biology of micrometastasis and metastatic progression;
- basic information about new therapeutic strategies for preventing metastasis formation through the identification of functionally relevant therapeutic targets that are frequently expressed on DTC. These targets might therefore be explored for the development of new forms of adjuvant cancer therapy aimed at specifically eradicating minimal disease with less severe side effects than current chemotherapy;
- a unique, large-scale biobank of freshly frozen and paraffin-embedded epithelial primary tumours and autologous samples of common sites of micrometastatic spread, including bone marrow (cells) and blood (cells and serum). The biobank will be complemented by computerised storage of data on patients and tumour characteristics, including histopathological analyses and clinical follow up information.

Potential applications

Apart from the ultimate goal of DISMAL (the delivery of an improved diagnostic platform for minimal disease detection), the sensitive detection tools might also be applied to a broad range of other biotechnology applications that involve the detection of rare cells. One field might be, for example, the screening for cancer cells in body fluids as a tool for primary cancer diagnosis, or more sensitive and specific detection of tumour cells in the lymph compartment.

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Keywords | DNA-methylation | breast cancer | prognosis | therapy prediction |

DNA METHYLATION

Epigenetic profiling of breast cancer: prognostic and therapeutic applications

Summary

Breast cancer is a genetic as well as an epigenetic disease. A prominent epigenetic alteration is DNA-methylation in the promoter region of a gene that prevents the gene from being expressed. Recently, high-throughput methods to analyse the methylation status of genes in a large number of samples simultaneously have been developed. We formed the present consortium, which encompasses members of the European Union and associated Member States, to take a multidisciplinary and innovative approach to study the DNA-methylation of breast tumours in order to improve the prognosis and treatment possibilities of the patients. The participating centres are contributing complementary state-of-theart proprietary technical expertise, large and well-documented tissue resources, and intense clinical expertise.

Problem

Today, the choice of treatment for individual breast cancer patients is based on a number of traditional clinical and pathological determinations. Stratification is not sufficient since approximately 90% of patients with lymph-node negative disease are grouped into a high-risk group and are consequently recommended adjuvant systemic therapy, even though it is known that only about 30% of node-negative patients will eventually experience disease recurrence. In addition, markers are needed that can predict which patient will respond to a specific type of systemic endocrine or chemotherapy, both in the adjuvant and metastatic setting.

Aim

To implement the epigenetic DNA-methylation analyses in the clinical setting to benefit both the individual patient by optimising their therapy concept, and the society as a whole by minimising treatment-related side effects and maximising cure rates.

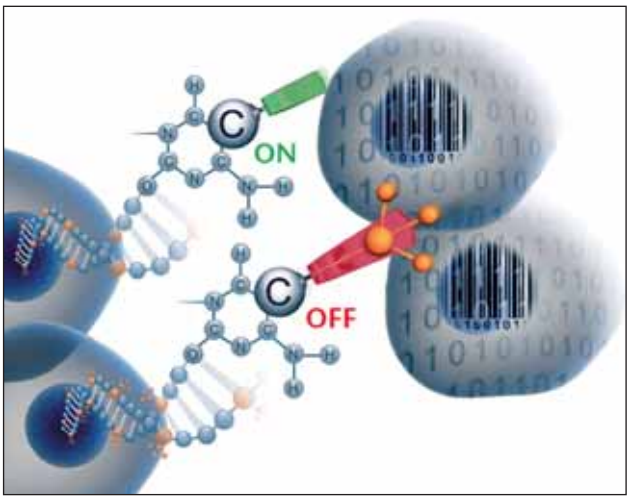
Expected results

The achievements expected are the improvement of patient prognosis by better risk assessment, and more specific therapeutic approaches based on newly developed targeted therapies and better therapy selection.

Potential applications

Methylation-based predictive tests are highly suited for clinical routine application since the DNA-based methodology is very robust in a routine setting as they can be accurately and sensitively detected in paraffin-embedded material. Large volume testing would be feasible for routine testing through an automated high-throughput approach.

The fifth base in the genome:
Methylation of the carbon 5 position is the epigenetic modification in the mammalian genome that contributes to cancer. © Epigenomics AG, Berlin.



Binary epigenetic predictor:
Predictive DNA methylation patterns identified during this project and indicated by the barcode here can guide the clinician to decide whether or not to treat and to determine the best type of treatment for the individual patient.
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Project number
LSHC-CT-2003-504586

EC contribution
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36 months

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01/01/2004

Instrument
STREP

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www.erasmusmc.nl/interne_oncologie/FP6/index.htm

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Keywords | Urology | clinical analysis | anticancer therapy | prognonsis | microarray |

Drop-Top

Integration of DNA, RNA and protein markers in a tool for the prognosis and diagnosis of human disease

Summary

The management of patients with superficial bladder cancer is difficult. No reliable means exists to determine whether a tumour will progress towards an infiltrative form, which requires radical surgery (cystectomy), or whether it will remain superficial, which requires only conservative surgery (resection). In addition, no dependable marker exists to predict whether a primary tumour will reappear or not during the years following surgical resection, forcing patients to undergo constant revisions that reduce their quality of life and overburden health care systems.

Numerous markers of various types (genes, transcripts and proteins) have been analyzed in bladder cancer studies. Some of them have been found to harbor potential for the prognosis (progression and recurrence) of superficial tumours. However, analyses have often been limited to a single type of marker or even to a single marker. To the best of our knowledge, no study has attempted to integrate different types of markers for an increased predictive power.

The main scientific goal of Drop-Top is to identify a set of markers with high predictive power for tumour progression and recurrence. To this end, we propose to collect tumour and urine samples from bladder cancer patients with a detailed clinical record, to measure in them markers of different types, to find statistically significant correlations between measurements and clinical records, and to select a predictor set.

In addition, Drop-Top pursues an ambitious technological challenge: the development of a prognosis microarray for the detection of said predictor set. In order to achieve this we propose to measure all three types of marker biomolecules by means of a single type of probe: oligonucleotides. Specifically, we propose to use short, long and aptamer oligonucleotides for the detection of gene, transcript and protein markers respectively.

Problem

Cancer is the second cause of death in the Western world and its incidence is increasing due to the overall aging of the population. Although advances in our understanding of the mechanisms of tumour onset and progression have been enormous, major impact on survival has been restricted to haematopoietic malignancies, some pediatric tumours, and very few solid tumours. Improvement in survival can be attributed not only to advances in standard chemo- and radio-therapy and to the recent implementation of targeted-drug therapy, but also to advances in diagnosis and the identification of high-risk groups, which allow for earlier and better treatment selection.

In contrast, the overall prognosis of the most common cancers, such as lung, colon, prostate, breast and bladder cancers remains poor, specially when the tumour cannot be cured by surgery. One limitation is that the pathologist's interpretation of the tumour's histological features remains the 'gold standard'. Recent advances in microarray technology together with information derived from the sequencing of the human genome have raised hopes that this situation will change dramatically in the coming years. For these hopes to be realized, it is essential to make appropriate use of information, technology and clinical resources. We believe that resources are often wasted because of inappropriate approaches and inadequate collaboration between clinical, academic and industrial partners.

Transcriptome analysis by DNA microarrays has been successfully used for the identification of biomarkers of tumour progression. However, and due to the use of different microarray platforms and patient selection strategies, among others, the biomarkers identified for a given clinical condition vary from study to study. Therefore, their application to common clinical practice has not yet taken place, and requires prospective studies. The Drop-Top proposal intends to overcome the above limitations by a double approach:

- prospective validation of the information acquired through retrospective studies. For this, a collaborative multicentre effort is essential;
- integration of biomarkers from genome, transcriptome and proteome analysis in a single predictor set. Even though each of these three analyses by itself will likely contribute, it is expected that the combination of biomarker types will result in an enhanced predictive power. This type of strategy has scarcely been used due to:
  - the high cost of microarray technology;
  - the need to have access to different platforms for the detection of different biomolecules;
  - the fragmentary nature of most of the published work (multiple DNA, mRNA and protein markers studied, but only individually and in most cases weakly associated to disease phenotype);
  - the lack of bioinformatics and biostatistics tools to handle heterogeneous data;
  - the limited amount of clinical and follow-up information usually available. In addition, most of these studies are performed without taking into consideration potential bias in the patient population under study (i.e. large tumour cases are more likely to be studied than small tumour cases for sample availability reasons).

Aim

Drop-Top has two major objectives, one technological and one scientific. Regarding the former, we propose to develop a tool for multiparametric analyses (mRNA levels, large genetic rearrangements, genetic mutations, genetic polymorphisms, protein levels and post-translational modifications) of biological samples, to better predict tumour progression and recurrence (see Figure 1). The evaluation of such heterogeneous parameters will be performed on a single microarray: the triple microarray, an oligonucleotide microarray for simultaneous DNA, RNA and protein assessment). The triple microarray constitutes the test surface of a workstation that integrates technology for the hybridization, scanning and detection of biomarkers. Its simplicity should facilitate a wide implementation of this tool in the clinic.

As scientific objective, we propose to identify a set of biomarkers with power for the prediction of clinical behaviour of bladder cancer. Selection of such set of biomarkers will be the end point of a five-phase endeavour:

- identification of candidate biomarkers for bladder cancer progression and recurrence from the scientific literature and from existing data generated by two Drop-Top partners specialized in bladder cancer;
- pre-selection of biomarkers on the basis of the strength of their association to tumour behaviour and on the scientific and technical quality of the study;
- measurement and validation of said candidate biomarkers in a set of samples from patients with a detailed clinical record and follow-up;
- application of bioinformatics and biostatistics tools for the identification of a set of biomarkers with a strong association to tumour behaviour.

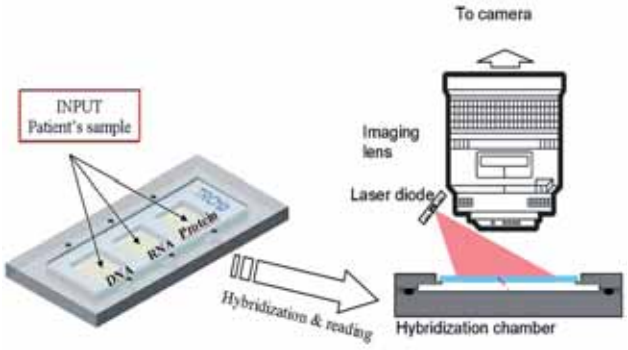

Figure 1 | Triple microarray and Integrated station for improved multiparametric analyses of biological sample.

The DroP-ToP strategy should be applicable to the study of any tumour type, and more generally to any disease with a genetic or gene-expression component. However, and as a proof of concept, we propose to apply it to bladder carcinoma because it represents a paradigm of the need for useful biomarkers in the clinical setting:

- it is one of the best models of tumour progression;
- its incidence ranks fifth among all cancer types (the fourth most common in males and the ninth in females);
- despite widely variable outcome, the diagnosis and prognosis tools used in the clinic are few and the same, and they are invasive even for asymptomatic patients (cystoscopy);
- it is the most expensive cancer type, as it can recur many times after treatment;
- its evolution is very difficult to predict, whereas the therapeutic approach for its two forms is completely different: when invasive at the time of diagnosis, it has a poor prognosis and requires aggressive surgery (cystectomy); when non-invasive, prognosis is favourable and it only requires conservative surgery (resection);
- its recurrence is also difficult to predict, which leads to unnecessary visits and cystoscopies for about 50 % of patients, whose tumours will never recur;
- a number of highly promising biomarker candidates have already been identified and reported in the literature.

Expected results

Cancer is the second leading cause of death worldwide. In the year 2002 there were 10 million new cases of cancer in the world, 6 million deaths and approximately 22 million people living with cancer worldwide. It is estimated that by year 2020 there will be 15 million new cases per year, and 10 millions deaths. Bladder cancer is a highly common neoplasia, mainly among men, and its incidence is rising in several countries in Europe. Approximately 125 000 new cases with bladder cancer are diagnosed each year in the EU.

Despite continued interest in the development of novel tests to better predict bladder cancer prognosis, there has been very limited progress. This is in part due to the fact that all tests developed until present are based on the detection of only one type of biomolecule (i.e. RNA, DNA or protein). Our approach is radically different: from a systematic review of current knowledge on biomarkers of bladder cancer and existing research results of the participating academic partners, we propose to develop a microarray that can detect the 3 major types of molecules in human biological samples. This should provide a much more solid basis to identify molecular predictors of the disease.

A Drop-Top research at work.

The Drop-Top proposed technology will bring about three main improvements:

- the number of invasive tests will be strongly reduced, leading to a reduction in costs by decreasing hospital admissions and the number of occupation hours lost;
- reduction in the number of invasive tests will also diminish morbidity and improve the quality of life of patients;
- a better prognosis will allow more adequate choice of treatment i.e. avoiding therapy to patients who do not need it and applying more aggressive therapy to patients at risk.

While most patients develop bladder tumours with a relatively good prognosis in terms of survival, their management is very expensive because of the multiple recurrences that most patients suffer, the need for invasive follow-up procedures, and the frequent hospitalizations. Overall, bladder cancer patients generate the highest cost/patient and lifetime among patients with cancer. In conclusion, bladder cancer generates very high costs to society.

At the present time, there is no test recommended or approved to help establish the prognosis of patients with bladder cancer. Over the past 10 years several products have been approved by the FDA for use in the early detection of bladder cancer recurrence (i.e. nmp22, BTA, Diagnocure Immunocyt, Vysis). However, none of these tests is yet used routinely in the clinical setting because they do not provide a substantial benefit. Therefore, there is a tremendous need for better tests.

Patients with bladder cancer develop multiple (up to 30) tumour recurrences, thus requiring continued follow-up after the initial diagnosis. For this reason, most patients undergo at least two medical visits over the first few years after diagnosis. Subsequently, the frequency of medical examinations varies according to the evolution of the disease. Therefore, a test that would allow the early detection of recurrences and an improved establishment of prognosis would be applied very frequently to the patients. The Drop-Top proposed test could even be used more commonly than cystoscopies are performed today given that it would not be invasive. Its availability would allow demonstration of the concept that early detection of tumour recurrence is associated with improved overall outcome.

Potential applications

Diagnosis and prognosis for the bladder cancer and others disease.

Preparation of the sample.

Project number
LSHB-CT-2006-037739

EC contribution
€ 1 834 331

Duration
36 months

Starting date
01/01/2007

Instrument
STREP

Project website
www.drop-top.net

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Keywords | Neuroblastoma | medulloblastoma | retinoblastoma | nephroblastoma | rhabdoid | Ewing | translational research |

E.E.T.-Pipeline

European Embryonal Tumour Pipeline

Summary

Treatment of embryonal tumours (ET) is a challenge for the pediatric oncologist. Innovative translational research is required to exploit available genomic data and implement state-of-the-art technologies to overcome the deficits of current diagnostic and treatment strategies. We will set up a Consortium of leading European institutions and SMEs with extensive clinical and technological expertise in order to establish a unique pipeline for the comprehensive development and validation of novel diagnostic tools in addition to efficient preclinical drug development for ET.

Our holistic approach includes:

- validation of a chip-based diagnostic platform tailored specifically for ET, including analysis of genes previously shown by the Consortium to be affected in ET;
- validation of a chip-based diagnostic platform tailored specifically for ET, including analysis of genes previously shown by the Consortium to be affected in ET;
- extension of an existing database designed to warehouse complete clinical and experimental data for neuroblastoma to include all ET entities;
- implementation of a virtual 'ET-Biobank' to improve sharing of patient samples;
- functional characterisation of the most promising molecular targets previously identified by the partners as a foundation for entry into a drug development pipeline;
- integration of existing disease-specific mouse models to evaluate new treatment modalities *in vivo*;
- initial evaluation of a screening method and antibody affecting ET cell invasion;
- application of novel bioinformatic solutions for meta-analysis;
- dissemination of the novel tools to researchers and clinical study centres in Europe.

Our coordinated effort can achieve the critical mass to facilitate the necessary integration of research capacities for translating ET genome data into significant medical progress. Involvement of clinical study centres will ensure a direct link to the bedside, aimed at improving child health and quality of life.

Problem

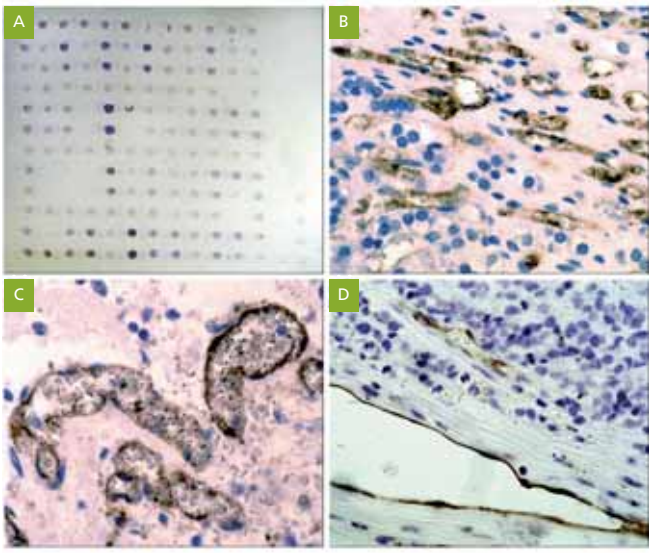
Second to accidents, cancer is still the leading cause of death for children in Europe. Approximately 30% of childhood malignancies are embryonal tumours (ET), often demonstrating resistance to conventional treatment approaches and being associated with lower survival rates compared to other childhood cancers. Thus, novel diagnostic and therapeutic options are urgently needed in particular for this group of tumours in order to improve survival rates and quality of life of pediatric cancer patients. The limitations of current treatment approaches include, in particular, a lack of validated post-genomic technology available for routine diagnostics and a large gap between target identification in basic research efforts and resulting pre-clinical development of novel drugs.

Beyond defining characteristic gene expression signatures, only a limited number of studies have addressed the functional analysis of identified target genes. The genetic low complexity of ET tumours provides a suitable system to identify druggable targets. Conclusive diagnosis using histology alone is difficult due to the uniform morphologies of the different ET entities, identifying ET as an important area to complement current strategies with modern post-genomic approaches.

Our approach is of particular importance for ET, as the ET entities are orphan diseases, meaning each entity does not have a large enough market to justify the costs of drug development by a private company. The identification of potential targets for all ET entities should be more economically attractive for private companies. Common molecular pathways such as myc- and RB-signalling and chromosomal deletions including 1p36 and 11q loss have been previously identified in different ET entities by the Consortium members and others, supporting a rationale integrating all ET types.

Aim

The multimodal genomic and proteomic approaches proposed here provide a promising alternative for more successful tumour diagnosis, subclassification and drug development for ET. This STREP will provide a coordinated strategy for the translation of basic research results into the pre-clinical arena, focusing on the implementation of state-of-the-art diagnostic tools, improvement of access to clinical material, and the efficient combination of post-genomic research approaches with pre-clinical drug development.



Custom-made tissue microarray for validation of identified novel target proteins in embryonal tumor tissue.

Project number
LSHC-CT-2006-037260

EC contribution
€ 4 000 000

Duration
36 months

Starting date
01/01/2007

Instrument
STREP

Project website
www.eet-pipeline.eu

Expected results

The E.E.T.-Pipeline provides a comprehensive, multi-team approach for improving ET diagnostics and treatment by the integration, assessment and validation of information generated by basic research utilising high-throughput technologies. In this integrated post-genomic research effort, we conceive dual pipelines concentrating on:

- state-of-the-art diagnostics;
- innovative drug development and pre-clinical testing, in order to channel these efforts. We aim to close the gap between basic and clinical research by focusing on the initial evaluation and characterisation of a selected subset of identified genes, proteins and biological pathways contributing to malignant transformation or progression of ET.

Potential applications

This integration of research capacities is expected to enable the participating SMEs to develop novel, biology-based therapies for disseminated disease, which will complement current protocols with more specific and less toxic alternatives. We aim to provide a platform to support the initial phase of development of new, well tolerated disease- and patient-adapted anti-tumour strategies.

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Keywords | Brain tumour diagnosis | DSS | MRS | genetic microarrays | HR-MAS |

eTUMOUR

Web Accessible MR Decision Support System for Brain Tumour Diagnosis and Prognosis, Incorporating *in vivo* and *ex vivo* Genomic and Metabolomic Data

Summary

Diagnosis and treatment of brain tumours is based on clinical symptoms, radiological appearance, and often a histopathological diagnosis of a biopsy. However, treatment response of histologically or radiologically similar tumours can vary widely, particularly for childhood tumours. 1H magnetic resonance spectroscopy (MRS) is a non-invasive technique for determining tissue biochemicals (the metabolomic profile). 1H MRS can be performed along with clinical MR Imaging but widespread use is hampered by specialised analysis requirements and poor dissemination of the skills needed to interpret the data. In addition, the genomic profile of tumours can be determined with DNA microarrays. eTUMOUR will bring together the expertise required to study the genomic and metabolomic characteristics of brain tumours, with a multicentre collaboration to acquire statistically significant data, particularly for rare tumour types. Based on these characteristics, a new web-accessible DSS will be developed, incorporating genomic and metabolomic data.

Problem

The lifespan of the European population is increasing and, accordingly, diseases that become prevalent in old age, such as brain tumours, will afflict a larger percentage of this population. Brain tumours do not have a lifestyle-associated etiology so prevention is not yet possible. Gold standard diagnosis is based on histological analysis of tumour biopsies, which is an invasive procedure that carries risks. Magnetic resonance spectroscopy (MRS) provides a non-invasive method to obtain a profile of the biochemical constituents of the tumour and has been shown to improve the accuracy of diagnosis in specific instances. However, MR spectra are complex and require skilled interpretation, hence routine clinical use of MRS is still low. A decision support system that provides an automated classification of MR spectra in terms of tumour type and grade should facilitate the uptake of MRS by clinicians. Tumour tissue is generally heterogeneous and there are a large number of different tumour types and grades. Thus to develop automated classification methods that are generally applicable, data from several hospitals must be combined to fully characterise the variability of tumour spectra. Furthermore, the possibility of using DNA microarrays to determine the tumour phenotype may create new subtypes not currently distinguished by standard histopathology. A more precise metabolomic analysis of tumour tissue is possible *ex vivo* by using MRS at high fields (> 11T) and this may further improve our understanding of the tumour biochemistry and may also refine the classification of brain tumours. To determine how the metabolomic and genomic profiles of tumours are related, and how they can be used to classify optimally individual tumours, requires a large database of both *in vivo* and *ex vivo* MR spectra and microarray analysis data. Finally, it is important to look for correlations of patient survival with these detailed tumour characteristics, to assess whether there are better prognostic indicators than those of the current grading system.

Aim

eTUMOUR aims to create a comprehensive web-accessible Decision Support System (DSS) for analysis and interpretation of magnetic resonance spectroscopy and imaging (MRS and MRI) data of brain tumours, which includes a database of clinical, histological and molecular phenotype data from brain tumour patients. The DSS will facilitate evidence-based clinical decision-making using MR and include new criteria such as genetic-based tumour classifications. The DSS will be also designed with agent technology to create a secure distributed database accessible trans-nationally by collaborating centres.

Expected results

- Development of a web-accessible Decision Support System (DSS) which has a graphical user interface (GUI) and a database of MRI/MRS, clinical, histological and molecular phenotype data (anonymised) from brain tumour patients.
- Facilitation of evidence-based clinical decision-making (for example diagnosis, prognosis, optimal treatment strategies, etc.) using MRSbased molecular imaging and incorporating new criteria, such as genetic-based tumour classifications, and related clinical information, such as patient outcome.
- Introduction of DNA microarray analysis of tumour biopsies as an adjuvant in tumour classification.
- Introduction of high field MRS of biopsy tissue to improve understanding of tumour biology, classification and grading, and to aid diagnosis and prognosis using new high field (3T) whole body MR systems.

Potential applications

Molecular imaging by MRS can potentially improve tumour diagnosis, aid in tumour delineation, as well as monitor response to treatment, and so can aid clinicians and neurosurgeons in the treatment of brain tumours. The MR DSS to

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LSHC-CT-2004-503094

EC contribution
€ 7 499 982

Duration
60 months

Starting date
01/02/2004

Instrument
IP

Project website
www.uv.es/etumour
www.etumour.net

be developed by eTUMOUR is likely to become a powerful tool for accurate diagnosis, prognosis and treatment selection and monitoring. The development of a web-based decision support system is innovative in itself and will promote the concept of how a multi-centre, web-distributed database of clinical information can be accessed, used and updated within healthcare systems with their unique and stringent constraints of data security and privacy. New criteria for classifying brain tumours will arise from eTUMOUR by determining the metabolomic and genomic profiles of tumours and relating these to prognosis and treatment response. Particularly significant will be the DNA microarray data, which may suggest the most appropriate genes to be used as markers for tumour classification and may lead to development of new or customised microarrays for routine clinical use. Genomic and metabolomic data is complementary to standard WHO pathological classifications. The combined molecular and clinical data is likely to produce a new and more complete methodology for classification and grading of all types of tumours and should also increase our understanding of tumour biology and its variation.

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Keywords | Diagnostics | glycome | blood | glycan | mass spectrometry | disease markers |

GLYFDIS

Glycans in Body Fluids- Potential for Disease Diagnostics

Summary

Developing effective tools to screen for cancer is an important endeavor and there is much research taking place to develop these tools. GLYFDIS project's objective is to develop methods for earlier diagnostic and effective disease screening of prostate and pancreatic cancer that will lead to better treatment outcomes. Early diagnosis of cancer is of far greater prognostic importance than any attempts to treat the disease in its late stages. Even in cases where the eventual outcome cannot be changed, treatment is simpler and quality of life improved for those cases where early diagnosis is achieved. For this purpose, GLYFDIS proposed a method of a simple noninvasive blood testing. Accurate monitoring of a cancerous state following diagnosis can significantly contribute to prognosis determination and on-line evaluation of therapeutic regimens.

The most widespread and diverse post-translational modification is glycosylation. The location and variation of glycans place them in a position to mediate cellular and intracellular signalling events, as well as participate in different biological processes including pathology states such as cancer. Therefore, we propose to use analyses of glycans for the diagnostics and monitoring of cancer.

Problem

Cancer is a significant burden on individuals, families and society. The economic impact of cancer is substantial. In 2002, the overall cost of cancer, as published by the National Cancer Institute, was 172 billion dollars. This does not account for the psychological toll that it takes on individuals and families.

Early detection and diagnosis of cancer is based on the observation that treatment is more effective when the disease is detected earlier in its natural history, prior to the development of symptoms, than in an advanced stage. Diagnosis of cancer in the early stages of the disease influences on many aspects of life. It can significantly decrease cancer-associated morbidity and mortality and to relieve the burden from patients, their families and the society. Accurate monitoring of a cancerous state following diagnosis can significantly contribute to prognosis determination and on-line evaluation of therapeutic regimens. Developing effective tools to screen for cancer is an important endeavor and there is much research taking place to develop these tools. The goal is to detect the cancer when it is localized to the organ of origin without invasion of surrounding tissues or distant organs.

The GLYFDIS project will make use of glycans. Its unique diversity compared to genome or proteome makes the glycans ideal for diagnosis and monitoring of cancer. Cancer-associated changes in the glycome of the tumoural tissue are very frequent. Currently the main hindrance could be the present glycome-analysis technologies that fall behind the rapidly developing genome- and proteome-analysing technologies.

The group hopes to develop a non-invasive method for the early diagnosis of prostate and pancreatic cancer based on glycan analysis.

Aim

GLYFDIS' main objectives are:

- To optimise high-throughput methods of glycan analysis for the diagnosis of prostate and pancreatic cancer by the analysis of glycans in blood.
- Identifying cancer associated glycome markers in serum samples of prostate and pancreatic cancer patients.
- Developing and validating protocols for lectin-based microarrays intended for large scale screening of cancer associated glycome markers in serum samples.

Expected results

- To identify biomarkers using glycomic and proteomic methods together with computer based algorithms.
- To develop a non-invasive, modest, diagnostic kit that will identify specific markers for cancer in the blood.
- Constructing a website and a glycome bio-bank integrating GLYFDIS results and serving as basis for a continuously growing public glycome data-bank.
- Dissemination of the information to the scientific community and community at large.

Potential applications

The project will generate knowledge relevant for non-invasive diagnosis of cancerous states with the effort in developing a standard protocol for diagnosis of serum samples.

Project number
LSHB-CT-2006-037661

EC contribution
€ 2 793 724

Duration
36 months

Starting date
01/11/2006

Instrument
STREP

Project website
www.glyfdis.org

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Keywords | Technological sciences | health sciences | physical sciences | medical imaging |

HI-CAM

Development of a high-resolution Anger camera for diagnosis and staging of cancer diseases based on state of the art detector technology

Summary

The purpose of the project is the development of a compact and high-resolution Anger camera to be used in clinical and research environments and which allows earlier and more reliable diagnosis and therapy planning of cancer diseases in specific applications where high overall spatial resolution (less than 3 mm) and system compactness (less than 10 x 10 cm^2 field of view) are required.

The gamma camera is based on the well-established Anger architecture, where a collimator acts as a mechanical sieve for incoming gamma photons, a continuous scintillator uses the energy of each selectively passed gamma photon to generate visible photons, and an array of photodetectors emits electric signals in response to the absorption of the visible photons. The improvement of performances is based on the use of a particular type of photodetector, the Silicon Drift Detector (SDD), which has recently demonstrated its ability to provide better performance, by comparison with commonly used photomultiplier tubes.

The camera is intended for use both single-handedly for planar scintigraphic studies and inserted in an annular holder (gantry) of small diameter for SPECT imaging. Thanks to its compactness and high spatial resolution, it offers potential applications in early diagnosis of cancer diseases affecting areas of the human body which can only be imaged with difficulty using the large and heavy imaging heads and gantries of commercial Anger cameras. The camera to be developed in the present project also offers promising perspectives of integration at the system level with MRI instrumentation, thanks to the relative insensitivity of the SDD photodetectors to large magnetic fields.

The research activity will be organised as follows: the first two years of the three-year project will be dedicated to the development of the SDD-based Anger camera, while the third year will be dedicated to the experimentation of the camera in selected imaging applications related to cancer diagnosis and research.

Problem

The state-of-the-art in the field is represented by a range of commercial systems, usually having large field detectors (~40x50 cm^2). These systems are best exploited while performing whole-body SPECT studies since their large, heavy PMT-based detector heads and bulky gantries present difficulties in operating close to the patient's skin for dedicated studies of specific, small tissues such as in parathyroid imaging, brain scanning and investigation of kidney cancer in infants. In a realistic clinical setting, at an imaging distance usually rather greater than 20 cm, the overall effective spatial resolution is typically 10-16 mm (7-10 mm for brain studies). When a single detector head is used for dedicated scintigraphic studies of small organs, permitting a closer imaging distance, the overall effective spatial resolution is limited by both the intrinsic spatial resolution of the system and the collimator.

Aim

The aim of the project is therefore the development of a new compact and high position resolution (<1mm) gamma camera based on the new SDD photodetector technology. The first technological objective is the development of an extended array of SDDs with large cell size (1 cm^2), characterised by high detection efficiency to the scintillation light and low electronic noise. The low noise level is a result of specialised advanced semiconductor processing, as well as of the integration of an on-chip JFET in the detector chip which allows us to fully exploit the intrinsic low capacitance of the SDD, by the minimisation of parasitic capacitances of the connection between detector and electronics.

The other key technological objectives addressed by the project are:

- the realisation of a high-resolution collimator. The aim is to obtain a parallel hole collimator whose spatial resolution equals ~2 mm at an imaging distance of 5 cm with a sensitivity higher than 20cpm/uCi. Pinhole collimators will be also realised;
- a very compact geometry of the detection module, based on a thin substrate where the SDD array and VLSI readout circuits will be assembled, and a single CsI(Tl) crystal (potentially substituted by the more recently introduced LaBr3:Ce) will be coupled to the photodetector array;
- the introduction of a thermoelectric system to attain moderate cooling (~ -20°C) during operation of the gamma camera;
- the development of dedicated VLSI electronics for amplification and filtering of the detector signals, followed by processing electronics based on FPGA for the event reconstruction;

- the design of a compact assembly of the complete Anger Camera. The compactness of the assembly will allow ease of positioning of the instrument close to the patient's body surface;
- the realisation of image-reconstruction algorithms and user interface software running on a common personal computer.

Expected results

- Development of large-areas low-noise Silicon Drift Detectors.
- Development of high-resolution collimators.
- Development of a high-resolution and compact Anger Camera based on state-of-the-art technologies.
- Improved diagnostic capabilities thanks to the use of the camera.

Potential applications

- Improved possibility to implement an effective therapy with higher capability to detect as small as possible concentrations of tumour cells.
- Effective imaging on reduced volume of the biological tissues: less than 10 x 10 cm^2 area of the planar view (in scintigraphic investigations with one single imaging head); less than 10 cm total extent on the coronal plane of the patient's body being imaged by the acquired scans (after appropriate rotation of the camera/s on the annular holder in the tomographic arrangement).
- Measurements on anatomical sites of the target which usually lead to severe space constraints during acquisition of the scan.
- Improved use of imaging instrumentation in those conditions where the patient's age, condition or physical disabilities (e.g. patient on wheelchair) prevent an effective use of large detector heads and gantries without compromising patient comfort.
- Brain tumours.
- Thyroid cancer, particularly differentiated carcinomas, with 99mTc-perthecnetate.
- Parathyroid cancer with 99mTc-sestamibi for preoperative localisation of parathyroid adenomas with the aim of surgical planning in MIP interventions (minimally invasive parathyroidectomy).
- Breast cancer with 99mTc-labelled lipophilic cations (Sesta-MIBI or tetrofosmin). The most promising application of the proposed system concern its use in preoperative or postoperative sites.

In addition, the project offers innovative approaches to the diagnosis of tumours in infants and children.

Project number
LSHC-CT-2006-037737

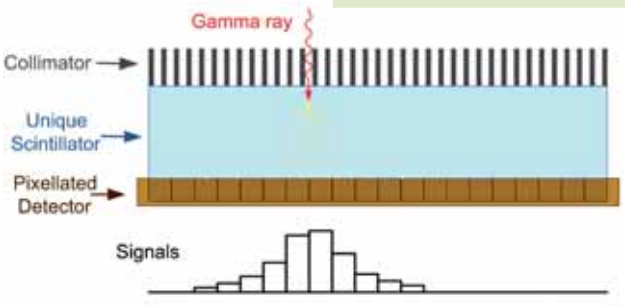
EC contribution
€ 1 715 000

Duration
36 months

Starting date
01/03/2007

Instrument
STREP – SME

Project website
www.hi-cam.org



Principle scheme of the Anger camera based on Silicon Drift Detectors technology developed in HICAM.

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Keywords | Mammography | breast imaging | photon counting | tomosynthesis | contrast mammography | breast cancer | dual-energy |

HighReX

High Resolution X-Ray Imaging for Improved Detection and Diagnosis of Breast Cancer

Summary

Breast cancer is currently the most common cause of death from cancer for women below 70 years of age, and currently over 100 million European women are screened every year for early detection through mammography. The objective of the proposal is to increase the efficiency in detection and diagnosis of breast cancer and thus to decrease the mortality in breast cancer.

To achieve this we will develop novel imaging methods based on recent results in the research fields of nano-technology, x-ray optics, detector technology and integrated electronics. The new modality, which will be designed by leading European industries and SMEs in these areas, will develop the only European detector platform for digital mammography commercially available today into a leading technology platform for tomorrow. The novel method will provide significantly increased contrast and spatial resolution, compared to current state-of-the-art breast imaging, through elimination of noise from electronics as well as from overlapping tissue and by way of utilising the signal more efficiently through fast single photon counting integrated circuits.

To make sure that the project targets the right issues in breast imaging, experienced mammography doctors from several European breast imaging centres are involved in the project and they will also test and evaluate the new imaging system and compare it to current state-of-the-art mammography, as well as ultrasound and MR imaging of the breast. The clinical trials will involve an enriched population of symptomatic women and the potential impact on European screening for and diagnosis of breast cancer will be estimated from the results.

Problem

The incidence of breast cancer currently increases in all European countries: according to the European Breast Cancer Network (EBCN), every year 50,000 women are diagnosed with breast cancer. Around 40 % of these women will die from the disease, making it the second most common cause of death for women between the ages of 20 and 70. The most efficient weapon against breast cancer is currently early detection through mammography screening. An early detection makes the subsequent therapy more successful and also mitigates bi-effects and facilitates breast conserving surgery in contrary to mastectomy. There is currently scientific evidence for a decrease of mortality of between 30 % and 40 % in the screened population.

Currently film is the most common image receptor in mammography, but this is now being replaced by digital mammography. In mammography screening, 70-90 % of the cancers are detected. The undetected cancers are mainly in women with dense breasts where the contrast resolution of state-of-the-art equipment is limited by overlapping tissue. Recent results from the so called ACRIN trial show that this challenge can to some extent be met with the advent of digital mammography. The improvements are however modest and the problem remains. What makes the problem worse is that the risk of breast cancer is almost a factor of three higher for women with dense breasts.

One way of solving the problem would be to increase the radiation dose to increase contrast resolution. However, in dense breasts, this would also increase the noise caused by overlying tissue. Moreover, the radiation dose in mammography is a growing concern, and increasing the radiation dose would mean an increased risk of radiation-induced cancers. This is particularly true for women below the age of 50 who, on average, have much denser breasts and who, because of their age, are significantly more radiation-sensitive compared to older women. Due to the limitations of the current technology, in many EU countries breast cancer screening is presently only offered to women older than 50.

Aim

We propose to solve the current dilemma in mammography by increasing the image quality in terms of contrast and spatial resolution while lowering the radiation dose. This will be achieved by using results from fundamental research in nano-technology, x-ray optics and detector technology obtained over the last few years. The only European detector platform currently available commercially for digital mammography will be drastically improved and developed into a detector system for the next generation of breast imaging equipment.

Expected results

An increase in breast cancer detection rate in screening of just 1% in Europe would mean that in the order of 500 otherwise undetected cases would be diagnosed annually, with a potential of 100-300 lives saved. It may however be expected that the increase in detection rate is significantly higher than 1%, maybe even exceeding 10 %.

Potential applications

We believe that the competitiveness of the European technology platform will manifest itself more strongly in the second generation of mammography and that the proposed project will be able to deliver a standard for 3D mammography that will be unsurpassed for quite some time to come. There is also no reason why the photon-counting advantages in mammography should not be beneficial as well in other imaging applications, such as CT and chest x-ray imaging. This project may provide the example needed for the technology to spread also to those areas.

Project number
LSHC-CT-2007-037642

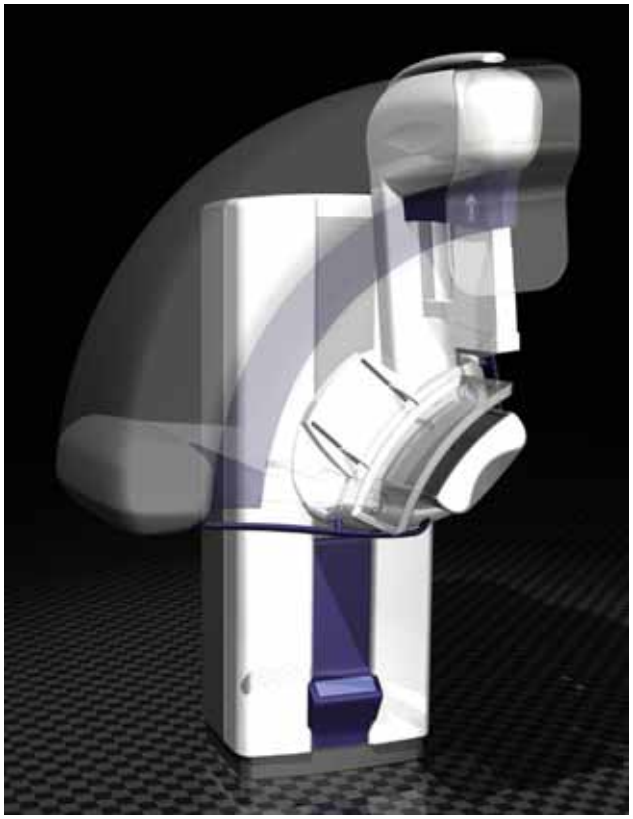
EC contribution
€ 3 635 200

Duration
36 months

Starting date
01/03/2007

Instrument
STREP – SME

Project website
www.sectra.se/medical/mammography/highrex



Vision of clinical application for breast cancer detection with 3D photon counting tomosynthesis based on research in the Highrex project.

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Keywords | Colon cancer | breast cancer | migrating cancer stem cells | mouse models | beta catenin | miRNA | kinome | phosphatome | single-cell analysis | epigenetics |

MCSCs

Migrating cancer stem cells (MCSCs) in breast and colon cancer

Summary

Carcinomas of the colon-rectum and breast represent among the most prevalent malignancies in the western world. A stepwise accumulation of genetic alterations in oncogenes and tumour suppressor genes is considered as the driving force behind tumour initiation, progression and metastasis.

However, although formally correct, this model does not take into account other essential characteristics of human cancers, i.e. tumour heterogeneity and the role played by a subpopulation of tumour cells, the cancer stem cells (CSCs), in determining local invasion into surrounding tissues and distant metastasis. Tumours are not autonomously acting proliferation machines, but are very heterogeneous, both in their morphological and functional aspects. In fact, an individual tumour shows distinct sub-areas of proliferation, cell cycle arrest, epithelial differentiation, cell adhesion and dissemination.

According to this more dynamic model (see Figure), the majority of tumour types, and in particular breast and colon cancer, arise within stem cell niches characterised by a tightly coordinated balance between self-renewal, migration, proliferation, differentiation and apoptosis. The initial and rate-limiting mutation affects this balance and leads to a relative increase in stem cells without drastically compromising their differentiation capacity. This imbalance eventually leads to the formation of a partially differentiated and heterogeneous tumour mass that, in response to additional somatic mutations and micro-environmental factors, progresses towards malignancy. Tumour cells are shed from this heterogeneous mass into the micro-environment. However, they will reflect the heterogeneity of the primary tumour, and only few will retain the necessary plasticity to undergo trans-differentiation and enable homing and metastasis in distal organs.

This 'Migrating Cancer Stem Cells' (MCSCs) model is central to our proposal and experimental plans. Our MCSCs consortium has been designed and assembled to address these issues by exploiting the unique expertise, experimental models and collections of human cancer samples of the different participants, in order to develop tailor-made diagnostic and therapeutic strategies for breast and colorectal cancer patients.

Problem

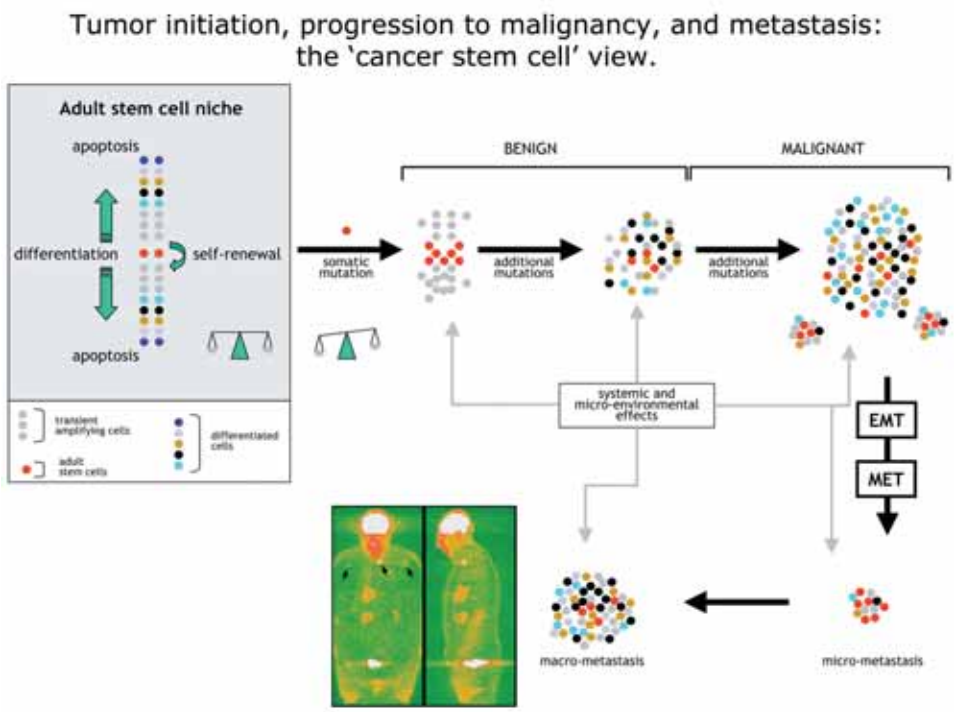
- Which signal transduction pathways underlie the onset of CSCs?
- Which additional genetic and epigenetic factors modulate their invasive behaviour?
- How does the tumour micro-environment, and therefore the cancer patient's genetic background, affect the capacity of MCSCs to successfully invade and metastatise distant sites thus determining good vs. poor prognosis?

Aim

- To prospectively isolate and characterise intestinal and mammary cancer stem cells.
- To elucidate the mechanisms underlying the aberrant behaviour of cancer stem cells during tumour initiation and progression to malignancy.

Expected results

- The isolation of intestinal and breast CSCs from both experimental mouse models and cancer patients.
- The establishment of expression, genomic and epigenetic signatures for CSCs and their micro-environment.
- The generation of new animal models for breast and colon cancer that closely reproduce the natural history of cancer stem cells and their progression towards malignancy and metastasis.
- The development of diagnostic and prognostic tests based on the early detection of MCSCs and the prediction of metachronous metastases in breast and colon cancer patients by specific antibodies.



Tumor initiation, progression to malignancy, and metastasis: the 'cancer stem cell' view.

Project number
LSHC-CT-2006-037297

EC contribution
€ 2 169 569

Duration
36 months

Starting date
01/11/2006

Instrument
STREP

Project website
www.mcscs.eu

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Keywords | HNPCC | familial gastric cancer | mismatch repair |

MMR-related cancer

Prevention, Detection and Molecular Characterisation of Mismatch Repair-Related Hereditary Cancers of the Digestive System

Project number
LSHC-CT-2005-018754

EC contribution
€ 2 620 200

Duration
36 months

Starting date
01/02/2006

Instrument
STREP

Project website
www.rug.nl/umcg/onderzoek/internationaleprojecten/europeseprojecten/mmr/index

Summary

This project focuses on hereditary cancers of the digestive system associated with microsatellite instability, hereditary non-polyposis colorectal cancer (HNPCC) and familial gastric cancer (FGC).
Microsatellite instability is the result of a defective mismatch repair (MMR) system. Germline mutations in MMR genes are found in families with HNPCC characterised by development of colorectal cancer and extracolonic malignancies, particularly cancer of the endometrium.
Evidence is accumulating that also a subset of FGC is MMR-related as families have been identified with tumours showing microsatellite instability. MMR gene mutations have not yet been identified in these families.

Problem

In HNPCC, identification of MMR gene mutations has helped in identifying individuals at risk when a clear pathogenic mutation was found.

Many families, however, in particular those with less penetrant HNPCC, remain genetically unresolved. Furthermore, in a large proportion of families, mutations are identified whose pathogenic nature is uncertain (unclassified variants). Although we have made great progress in the genetic delineation of this cancer syndrome, it has scarcely improved early diagnosis or treatment of cancer.

Aim

The objectives are to improve genetic testing by:

- determining the role known MMR genes play in both cancer syndromes and identifying new HNPCC or FGC-related genes;
- setting up comprehensive functional assays to determine the role of unclassified variants in MMR related genes;
- identifying tumour cells at very early stages in faeces by enhancing the sensitivity of MSI determination;
- profiling mutations accumulating in tumours as a consequence of MMR deficiency, in order to get a better insight in tumour development, which can be instrumental in clinical management/tumour treatment.

Expected results

Our proposal will thus improve genetic testing, improve early detection of polyps/tumours in individuals at risk for these cancer syndromes and improve clinical management of HNPCC and FGC patients.

Potential applications

The assays and the data generated will be set up and used in diagnostic laboratories and by clinical geneticists all over Europe and the world.

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Keywords | Pancreatic cancer | molecular diagnostics | molecular imaging | early diagnosis | PanINs |

MolDiag-Paca

Novel Molecular Diagnostic Tools for the Prevention and Diagnosis of Pancreatic Cancer

Problem

Pancreatic cancer, molecular diagnostics, molecular imaging, early diagnosis, PanINs Problem Pancreatic cancer has a dismal prognosis due to the late presentation of the tumours and the absence of satisfactory therapeutic options for advanced disease. Surgical resection of early tumours or preneoplastic lesions represents the only curative approach. It is currently difficult to identify early stages of the tumour and preneoplastic lesions and, once in an advanced stage, there are no diagnostic means for a risk stratification of patients concerning prognosis or responsiveness to therapy.

Aim

Here we propose an integrated project joining leading groups in European pancreatic cancer research, SMEs and industry to develop novel molecular diagnostic approaches for the prevention, early diagnosis and risk stratification of pancreatic cancer.

Expected results

These approaches will be developed based on large-scale transcriptome, genome and proteome analyses that have been performed by members of the consortium in recent years in two subsequent EUfunded concerted actions. Within these concerted actions, the relevant protocols and processes were optimised and adjusted between the partners and common standards, as well as establishing a network of clinicians, clinical research and basic research groups. From this basis, novel molecular techniques will be developed for the detection of cancer cells or preneoplastic cells in minimal amounts of clinical tissue (fine needle biopsies) or fluid (pancreatic/duodenal juice or serum) samples.

Potential applications

Novel tools will include transcript and epigenetic analyses, chip technology, single or multiple marker protein studies, DNA/RNA PCR analyses, serum proteomics and molecular imaging. The project will use clinical samples such as serum, urine, fine needle aspirates and surgically resected materials of pancreatic cancer patients collected in large multinational European trials such as ESPAC and EUROPAC. During the last phase, prospective clinical trials of novel diagnostic tools developed in the integrated project will be designed and started.

Project number
LSHB-CT-2006-018771

EC contribution
€ 8 500 000

Duration
36 months

Starting date
01/08/2006

Instrument
IP

Project website
www.moldiagpaca.eu

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Keywords | Cancer | cancer screening | capsule endoscopy | biosensing |

NEMO

Nano based capsule-Endoscopy with Molecular Imaging and Optical biopsy

Summary

Gastrointestinal (GI) malignancy imposes a significant impact on the well-being of the European members. Ageing of the population means that death rate will continue to rise. A report of the IARC (France) indicates insufficient compliance to colorectal cancer prevention programs, due to the lack of a simple, patient friendly diagnosis method.

The objective of the NEMO project is to develop an advance cancer screening method friendly enough to significantly increase compliance , simplify the diagnosis procedure and increase the sensitivity and specificity of early detection. The concept of the NEMO approach is to combine capsule endoscopy with nano-based molecular recognition that will highlights cancerous and precancerous lesions in the GI tract thus considerably increases the accuracy and ease of diagnosis. The system will merge few technological platforms: Nanotechnology for targeting and marking the infected organ, Capsule Endoscopy to detect the marked disorder, Capsule manoeuvring technologies to move the autonomous NEMO capsule backwards and forwards in the gastrointestinal tract, as well as miniaturization and low power technologies.

A major task of the project is to develop nanocontainers, labelled with targeting agents and filled with dyeing material. The administered nanocontainers will be tailored to react with the target and mark the infected organ. Another task is to develop a capsule based on Narrow Band Imaging. This advanced capsule will provide both: visual images of the GI tract and molecular characterization of the disorder. Fusing image and molecular information together, a new medical tool for early cancer detection with high sensitivity and specificity will be developed.

Problem

Earlier detection of cancer using screening methods is likely to be the most practical way of addressing the epidemic of gastrointestinal cancers. Gastrointestinal cancers are detected mainly by gastroscopy or colonoscopy followed by biopsy. There is good evidence that such screening can find early cancers and that lives can be saved if such early cancers are discovered and removed. Many patients however are reluctant to have screening gastroscopies and colonoscopies because of the discomfort of the procedures. Women especially are reluctant to undergo screening colonoscopy.

The acceptability of capsule endoscopy, which is pain free, requires no sedation and does not necessarily entail a hospital visit, is attractive for patients. It is likely that they would find such a screening method much more acceptable than screening colonoscopy for example.

It would be very helpful if capsule endoscopic video imaging could be combined with more sensitive and specific methods for detection of early cancer to avoid the need for biopsy.

Aim

The aim of the NEMO project is to develop a new advanced cancer screening method friendly enough to significantly increase compliance, simplify the diagnosis procedure and increase the sensitivity and specificity of early detection. The system will miniaturize and merge a variety of technological platforms: Nanotechnology for targeting and marking the precancerous tissue capsule endoscopy and capsule manoeuvring technologies to detect the marked disorder. By fusion of image with data of molecular analysis a new medical diagnostic tool may be formed. The use of specific optical filters used in conjunction with light emitting diodes (LEDs) will be explored to make a miniature narrow band imaging device which can be contained within a capsule endoscope. Narrow band imaging reduces the surface reflection of broad band illumination and can allow small or flat precancerous lesions to be seen clearly when they are difficult to see with conventional illumination. The combination of conventional and narrow band imaging may be able to provide an overview of the gastrointestinal tract indicating one of many sites of interest. It could be alternated with conventional imaging.

Expected results

It is expected that the new Capsule Endoscopy screening method will provide information on the presence or absence of cancerous or precancerous situations with high sensitivity and specificity. We hope to develop a combination of miniature spectral and Magnetic Resonance nanotechnology to create 'virtual biopsy' methods and incorporating these within the capsule endoscope.

It is also expected that the new autonomous NEMO capsule will be able to move backwards and forwards in the gastrointestinal tract, for example to re-examine a suspicious lesion.

Potential applications

Conventional endoscopies are usually performed in hospitals; require trained doctors and a nursing staff for monitoring and cleaning the equipment. Endoscopy generally requires insufflations to expand the folds of tissue and enhance examination.

Project number
LSHB-CT-2006-037362

EC contribution
€ 2 832 020

Duration
36 months

Starting date
01/11/2006

Instrument
STREP

Project website
http://fcs.itc.it/NEMO/

The procedure is usually associated with sedation because it is painful or at least uncomfortable for the patient and requires time off work to recover from the anaesthesia. Anxiety about the discomfort of endoscopy, especially of colonoscopy, greatly reduces the uptake by patients offered this type of cancer screening.

The aim of the NEMO project is to develop a system offering an improved clinical solution; Wireless capsule endoscopy is painless, does not need to be administered in hospital and does not require a team of nurses to clean the devices since it is disposable, nor does it require great skill to perform (although skill in interpretation of the images is needed). Thus it addresses the private clinics as well as institutions.

The main applications will be to replace FOBT, colonoscopy or gastroscopy as first line screening methods.

The combination of wireless capsule endoscopy with advanced optical technologies is likely to make earlier detection much easier and more effective than current flexible endoscopic technologies.

Moreover, combining its capability to analyze secretions with the localization, the solution offers Pancreatic and liver cancer detection as a by-product of stomach screening.

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Keywords | Ovarian cancer | molecular diagnosis | minimal disease | chemotherapy | gene expression | signature | proteomics | CGH | mutation | methylation | targeted therapy |

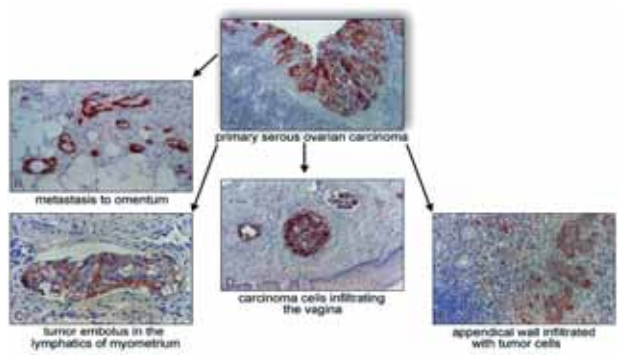
OVCAD

Ovarian Cancer – Diagnosis of a Silent Killer

Summary

In Europe each year, 63 000 ovarian cancer cases are diagnosed and 41 000 ovarian cancer patients die. Seventy-five per cent of patients are diagnosed at advanced stages due to an asymptomatic course and 75% of these patients die within five years. Treatment involves surgery followed by chemotherapy. However, 25% of patients relapse within six months after initial treatment and there is doubt as to whether these patients benefit from this therapy at all. Recurrent disease is diagnosed by clinical evidences or by CA125 dynamics. But detection is limited due to a lack of sensitivity and specificity, as is the case with primary diagnosis.

Currently, there is no method to detect minimal disease, the first indicator of therapy failure and a precursor of recurrence, which inevitably leaves specific traces throughout the body. There is a strong need for molecular-oriented research to detect minimal disease in order to disburden patients from an inefficient and toxic therapy.



Ovarian carcinoma – immunohistochemical staining of L1on ovarian carcinoma and its metastases in adjacent organs (Source: J. Sehouli, Berlin; M. Fogel, Rehovot and P. Altevogt, Heidelberg).

Problem

Diagnosis at advanced stages and a high mortality rate is the tragedy of ovarian cancer. After initial surgical therapy, 25% of patients relapse within six months and 75% die within five years, mainly due to resistance to chemotherapy. Available methods for the detection of recurrent disease lack both sensitivity and specificity and usually miss minimal disease as a first sign of therapy resistance.

Aim

The aim of this project is to define clinically useful molecular-orientated early detection of minimal residual disease (MRD) in ovarian cancer that can identify patients not responding to the standard (state-of-theart) therapy at the time of surgery. This will disburden the patients from the very toxic and inefficient standard chemotherapy and eventually lead to alternative therapy modalities, which can really bring benefits to this group of patients. 'Signatures' that signal the presence of MRD will be investigated at various molecular levels (DNA, RNA and protein) and in a broad spectrum of biological materials (tumour tissue, disseminated tumour cells, sera, white blood cells, ascites) from ovarian cancer patients.

Specifically, the project is aiming at:

- development and/or validation of several molecular diagnostic methods to identify MRD in ovarian cancer patients;
- definition of a new 'diagnostic state-of-the-art' by correlating the diagnostic results with the clinically-defined response of the patients to standard therapy, consisting of primary surgery, followed by standard platinum/Taxol-based chemotherapy;
- early discovery and characterisation of MRD by molecular diagnostics leading to additional therapeutic interventions, ultimately improving patients' prognosis and quality of life;
- better understanding of the mechanisms that cause MRD and therapy failure;
- identification and evaluation of new potential therapy targets.

Expected results

Definition of a diagnostic method consisting of one or several molecular tests for early detection of minimal disease as an early indicator of therapy failure.

Potential applications

Diagnostic molecular tests and immunotherapy.

Immunohistochemical staining of disseminated tumour cells isolated from blood

- Comparative genomic hybridisation to detect genomic loss and gain.
- GeneStiX Imager for analysis of gene methylation (Sources: G. Hager and R. Zeillinger, Vienna; C. Theillet, Montpellier; Biofocus GmbH, Recklinghausen).

Project number
LSHC-CT-2005-018698

EC contribution
€ 4 259 625

Duration
36 months

Starting date
15/12/2005

Instrument
STREP

Project website
www.ovcad.org

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Keywords | Prostate cancer | markers | diagnosis | prognosis | serum | urine | proteomics | mass spectrometry |

P-MARK

Validation of recently developed diagnostic and prognostic markers and identification of novel markersfor prostate cancer using European databases

Summary

The current diagnostic markers for prostate cancer have a low specificity and lead to over-diagnosis and over-treatment due to the detection of small non-aggressive or non life-threatening cancers. In addition, there are currently no efficient serum or urine markers available for the prognosis of this malignancy. The P-Mark project will address the growing need for improved diagnostic and prognostic markers for prostate cancer.

Problem

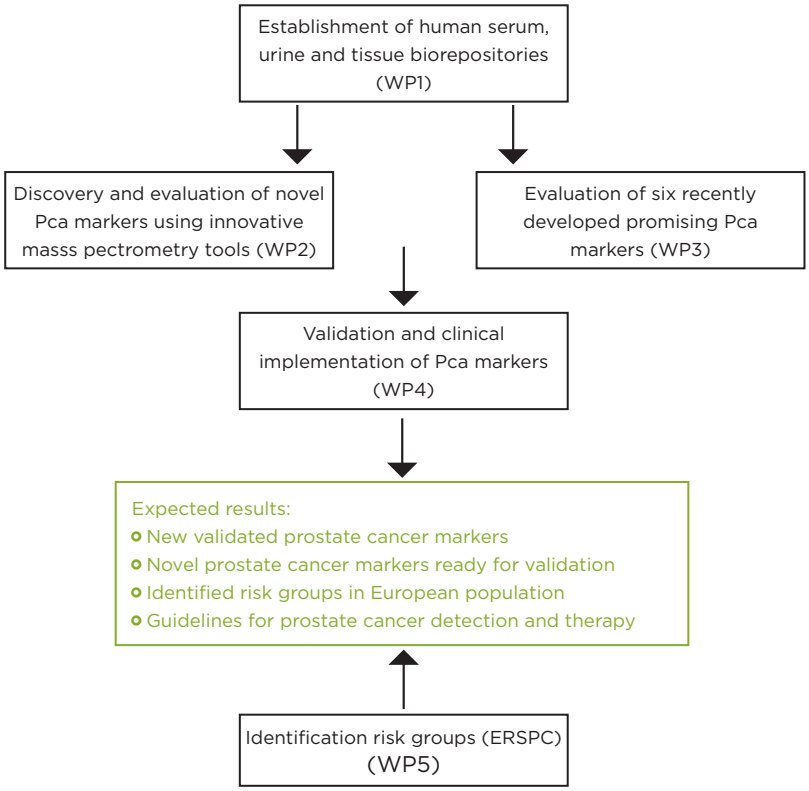
In Europe, prostate cancer (Pca) is the second most frequent lethal malignancy in men. Yearly about 40 000 men die of Pca in the EU countries. There is a slow increase of mortality and in addition, due to an ageing population, a 50% increase in incidence is expected by 2020. So far, the only chance for cure is early detection and treatment by either surgery or radiotherapy. Diagnosis of Pca is made by ultrasound-guided transrectal biopsy of the prostate for histology. An increased level of the serum marker prostate specific antigen (PSA) often signals the presence of prostate cancer and the need to perform such a biopsy. A major disadvantage of this diagnostic marker is its low specificity, resulting in a significant amount of false biopsy indications. PSA is a normal excretion product of the prostate cells and is therefore not only found in the circulation of men with prostate cancer but also of men with a normal prostate and men with benign prostatic hyperplasia, a phenomenon that is associated with ageing. Nevertheless, PSA is the standard marker for Pca diagnosis and has been demonstrated to be effective in advancing the diagnosis by detecting Pca at earlier stages. A growing number of men choose to be screened for Pca by PSA analysis, even up to 60-70% of men in the USA. However, the value of screening for Pca has not been established yet and is currently the subject of investigation in the European Randomised Study of Screening for Prostate Cancer (ERSPC). A major drawback of the standard diagnostic tools for Pca is the detection of small non-aggressive or non life-threatening cancers, leading to over-diagnosis and over-treatment, as well as the detection of tumours that are too advanced to cure. Currently, there are no serum or urine markers available for the prognosis of Pca at early disease stages apart from PSA. It is apparent that improved diagnostic and prognostic serum or urine markers are required that can discriminate men with clinically irrelevant Pca, curable Pca, or life-threatening Pca.

Aim

For three years, P-Mark will search for improved diagnostic and prognostic Pca markers by the identification and evaluation of novel markers as well as the evaluation and validation of recently developed promising markers. Novel serum and urine markers will be identified in clinically well-defined biomaterials using innovative mass spectrometry tools, and antibody-based immunoassays will be developed for these markers. The novel markers will be evaluated for their clinical importance using these assays. Recently developed, promising markers that prove their clinical value during the evaluation will be validated on a sample set derived from two European screening studies (the ERSPC study and the ProtecT study). Eventually, the markers arising from this project will be offered to SMEs for commercialisation and to ongoing large European clinical studies for clinical implementation.

Expected results

- The establishment of a serum biorepository and a urine biorepository for the discovery, evaluation and validation of diagnostic and prognostic Pca markers.
- The discovery of novel Pca markers in human body fluids by innovative mass spectrometry tools.
- The establishment of the clinical utility of recently developed promising Pca markers, including PCA3DD3, bone morphogenetic protein-6 (BMP-6), osteoprotegerin (OPG), nicked PSA, human kallikrein 2 (hK2) and cytochrome P450 3A5*3 polymorphism (CYP3A5*3).
- The validation of Pca markers and identification of risk groups in the general population in Europe.
- The development of guidelines for cost-efficient strategies for Pca detection and therapy.



Project number
LSHC-CT-2004-503011

EC contribution
€ 3 480 764

Duration
48 months

Starting date
01/11/2004

Instrument
STREP

Project website
www.p-mark.org

Potential applications

P-Mark will evaluate the clinical value of recently developed promising Pca markers and of novel Pca markers. If a marker meets the defined P-Mark marker criteria (improved sensitivity and specificity over current markers for diagnosis or prognosis; indicative for early detection, over-treatment, risk for progression or therapy resistance; clinically relevant target in relation to tumour biology; reliable and cost-efficiently determinable in non-invasively obtained specimens; stable component in specimen), it will be developed further for the validation in a monocentre or multi-centre setting. In addition, the marker will be offered to commercial enterprises for commercialisation. Validation will lead to guidelines for cost-efficient strategies for detection and treatment as well as recommendations for marker application, that have to be discussed in the public domain of related European professional societies. Validated markers will be offered to the principal investigators of ongoing screening studies in Europe for implementation in the study. Taken the duration of P-Mark into consideration (three years), clinical marker implementation will continue beyond this project.

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Keywords | Lung cancer | point of care | quantum dots | UV light source | flash lamp | fluorescence | immuno-diagnosis | multiparameter | blood separation | expert system | molecule coupling | luminescent tags |

POC4life

Multiparametric quantum dot bioassay for point of care diagnosis

Summary

This project aims at improving the healthcare of patients by elaborating a unique POC diagnosis platform which will help specialists to deliver an earlier diagnosis and to decide for appropriate treatment. The goal is to provide the clinicians with multiparametric measurement of the main 4/5 essential markers and to support decision with a software tool. This will be a cost-effective breakthrough in the diagnosis market.

Problem

Each year 377 000 new European citizens develop lung cancer and 340 000 die from it. Studies show that early diagnosis and accurate cancer typing could save number of lives. Laboratories nowadays have a wide panel of reproducible diagnostic tests at their disposal: these are mostly routine tests realised in centralized laboratories. The needs for early diagnosis, multiparametric analysis of results and quick monitoring of disease progression or therapeutic sensitivity were progressively left aside, whereas they could be fulfilled with using decentralised diagnostic tools, close to the patient.

Among the possible applications of this new concept, the partners have chosen to work on the primary diagnosis of the histological types of lung cancer to help to give an improved initial diagnosis and to eliminate the 15-20 % problematic or late diagnosed cases. The study will pay special care to women (lung cancer death rates for women have been still increasing in Europe since the 1990s and marker patterns may be different). It will then have a huge impact on health by contributing to the fight against cancer and the development of gender dimension in research. For this purpose, the multidisciplinary project will involve academic researchers (from Germany, Spain and France) and SMEs (from Sweden and the UK) gathering around the initiators of the project (the SME CEZANNE, the University of Strasbourg in France and the University of Potsdam in Germany) which have the skills to build a multiparametric device, to develop immunoassays and to design an interpretation software.

Aim

Objective 1: Elaborate an innovative medical device: a unique point of care diagnosis platform which will help specialists to make earlier diagnosis and provide more appropriate treatments.

Objective 2: Provide the best possible integration of parameters by means of a consortium composed of public and private partners such as research intensive SMEs and academic entities Europe-wide.

Objective 3: Elaborate the new device for a specific application: the primary diagnosis of the different types of lung cancer. The project will then have a huge impact on health by contributing to the fight against cancer and the development of gender dimension in research.

The objective of the project is to generalize this approach to combinations of immuno-assay measurements to deliver a clear diagnosis of the disease or monitoring information. The generalization means first that the diagnosis should be accessible to various types of medical practices (medical doctor to hospitals) and thus a low cost , easy to use 'Point of Care' (POC) device should be developed. However this should not be done to the detriment of quality and precision. A homogeneous technology known for high level precision can therefore be a judicious choice. Generalization means also that various pathologies could be addressed: typically from 2 to 4 or 5 immuno-assays. We thus aim at allowing on the POC device the simultaneous measurement of 4 to 5 immuno-assays with one draw of patient sample (1 droplet). Finally generalization means universality of the measurement technique and of the data reduction process. In this way, fluorescent measurement based on FRET (Fluorescence Resonance Energy Transfer) seems an excellent choice, since it may be extended in the future to other diagnostics such as DNA analysis, coagulation, microbiology...

Project number
LSHB-CT-2007-037933

EC contribution
€ 2 497 815

Duration
36 months

Starting date
02/01/2007

Instrument
STREP

Project website
www.poc4life.eu

Expected results

The project should reach the following challenging objectives:

- develop a functional prototype of POC multi-parametric measurement for immuno assays, based on Homogeneous Time Resolved Fluorescence (HTRF), for which main characteristics are: equivalent to a A4 sheet of paper, cost of less than 2 000 Euros, works with a sample droplet deposited on a disposable reagent vessel containing dried reagents;
- define the panel of assays and how to combine them into a decision making software (to be developed).

Potential applications

Multiparametric diagnostics in the following fields:

- cancer;
- prenatal diagnostics;
- sepsis;
- cardiac.

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Keywords | Prostate cancer | micrometastasis | minimal residual disease | bioluminescence | multiphoton microscopy | nanotechnology | optoacoustic technology | detection | treatment | MegaFasL | human glandular kallikrein 2 |

PROMET

Prostate cancer molecular-oriented detection and treatment of minimal residual disease

Summary

In the European Union, about 200 000 men are diagnosed with prostate cancer every year and that number is likely to increase due to a growing population at risk due to ageing. Because of the progress made in the treatment of the primary tumour, mortality in cancer patients is increasingly linked to metastatic disease, often hidden (micrometastasis or 'minimal residual disease') at the time of diagnosis/therapy of the primary tumour. Understanding the complex mechanisms of metastasis (circulating tumour cells – micrometastasis – metastasis) at the molecular and physiological level is crucial for the successful detection of minimal residual disease and for evolving possible strategies for the prevention of their development into overt metastasis.

In this project, we intend to elucidate the mechanisms and signature of minimal residual disease in prostate cancer and develop novel therapeutic approaches to prevent the development of minimal residual disease to overt metastasis. In close collaboration of basic scientists with clinical researchers, the pathways of minimal residual disease will be explored using functional genomics and expression profiling as technology platforms, advanced experimental models of minimal residual disease using bioluminescence, multiphoton microscopy, nanotechnology and optoacoustic technology for detection and treatment. Innovative imaging and therapeutic strategies developed by the industry and selected for their potential to enhance detection and eradicate minimal residual disease will be tested in preclinical models for subsequent clinical evaluation.

The goal is to identify at least two signal transduction targets, to develop a diagnostic test for the detection of the presence of minimal residual disease and to define a novel therapeutic strategy for the treatment of this disease in prostate cancer. Thus, earlier detection and diseasespecific treatment may decrease morbidity and mortality, and ultimately have an impact on socio-economical costs.

Problem

Prostate cancer is one of the most common malignancies in men: in Europe approximately 40 000 men die of it each year. Due to the aging population, this number will increase significantly to around 60 000 men by the year 2020. Therefore, prostate cancer is a major medical problem with which the European Community will be increasingly confronted in the forthcoming decades. There are a number of initiatives ongoing to reduce the mortality by detecting the disease earlier, the so-called screening programmes.The clinical evaluation of the usefulness of prostate cancer screening is being examined in the European randomised study of screening for prostate cancer and is expected to answer this question sometime in 2006. Even though there is a significant stage migration in the patient population identified with this disease, mortality has still not dropped in Europe.

This is primarily because when the tumour has locally spread, no curative intervention is available. If the patients are given the time to live, they will ultimately develop bone metastatic disease that is unresponsive to the currently available androgen ablation-based therapies. Bone metastases cause considerable morbidity characterised by severe bone pain and high incidence of skeletal, neurological and haematopoietic complications (hypercalcaemia, fracture, spinal cord compression and bone marrow aplasia). These, together with the chronic character of terminal CaP disease, have a severe impact on the socio-economical costs for healthcare.

The objective of this project therefore meets directly with one of the priorities of the life science health programme, namely to combat a major disease, in this case prostate cancer. Prostate cancer is rather unique in its clinical behaviour and its molecular genetic background. Relatively few consistent mutations have been found, which do not occur in other cancers, so many cases of indolent tumours are described.

Aim

Because of the progress made in the treatment of the primary tumour by surgery or radiotherapy, mortality in cancer patients is increasingly linked to metastatic disease. Malignant tumours are known to be heterogeneous, and subpopulations with different invasive and metastatic potential may alter their biological properties over time and under treatment due to genetic instability and epigenetic influences.

The primary tumour releases a large number of cells into the blood stream. However, only a small minority (approx. 0.01%) of the tumour cells entering the blood are thought to be capable of developing into metastatic deposits. The future ability to detect minimal residual disease early, to understand the natural history of micrometastasis and, consequently, to predict outcome, and ultimately to treat adequately will rely on investigational efforts in a context as close as possible to the clinical situation. For this a close interaction between clinical experience and basic research, together with the availability of human tumour tissue specimens from established tumour tissue banks and adequate experimental models are crucial to improve current treatment modalities or even develop innovative therapeutic strategies. In this targeted approach to combat minimal residual disease in prostate cancer, we will pursue various levels at which we attack the malignant process and validate these at a phenotypic and functional level. We will be developing novel means of detecting and treating minimal residual disease. By integrating a variety of state of the art approaches, we aim to:

- identify and validate at least two target genes for detection of minimal residual disease in prostate cancer;
- develop an integral *in vivo* model of minimal residual disease allowing the study of the mechanisms and signatures;
- evaluate the *in vivo* detection of minimal residual disease by means of nanoparticles and optoacoustics;
- develop a therapeutic strategy for the treatment of minimal residual disease in prostate cancer.

Expected results

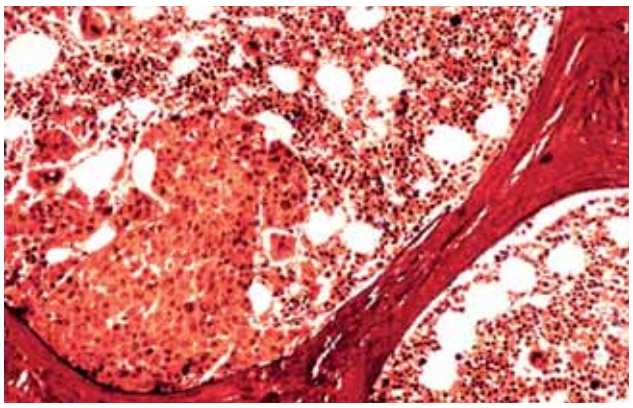
We expect to identify genes up- or down-regulated in minimal residual disease with a potential for use in diagnostics and therapeutic strategies. Furthermore, the expression pattern might increase our understanding of the mechanisms and reveal potential novel therapeutic targets. With this work we expect to provide a detection assay with the potential for use in clinical practice based on blood, urine or bone marrow aspirate and evidence that optoacoustics can be applied in the clinical context.

Novel treatment strategies will be developed and we expect to validate at least one treatment strategy in the treatment of minimal residual disease (MRD) that can be applied in the clinical setting. Finally we expect to establish a confocal and deconvolution-based dorsal chamber metatarsal model for the study of homing and growth support of minimal residual disease. Further we intend to establish a dual wavelength bioluminescent imaging system for the simultaneous study of two indicators, enabling the evaluation of the interrelation between these.

Potential applications

The innovative potential and impact on industry, the health system and the market lies in:

- the development of novel diagnostic methods for the detection of minimal residual disease;
- the implementation of optoacoustics with the help of nanoparticles for diagnosis and therapy;
- novel targeted therapeutic strategies for micrometastases that take into account the particular knowledge about specific biology of the disease gained from animal models that more closely mimic MRD (translational research);
- the optimisation of experimental imaging of living cells by coupling multi-photon microscopy with quantum dot nanoparticle cell tracking to study early pathophysiological pathways involved in MRD. This will complement other methods used by the group, such as whole body animal bioluminescent imaging;
- the development of a more sensitive bioluminescence-based imaging system for the preclinical investigation of the biology of minimal residual disease and the *in vivo* evaluation of novel diagnostic and therapeutic methods.



Micrometastasis in the bone marrow.

Project number
LSHC-CT-2006-018858

EC contribution
€ 4 034 200

Duration
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Starting date
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Instrument
STREP

Project website
www.fp6-promet.net

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Keywords | Ewing's sarcoma | EWS/FLI1 | CD99 | insulin like growth factor | microarrays |

PROTHETS

Prognosis and therapeutic targets in the Ewing family of tumours

Summary

The project through collaborative studies will define prognostic markers and new therapeutic targets in the Ewing's sarcoma family of tumours (ESFT) to provide rigorous scientific justifications for the development of clinical trials for this rare disease, which is mainly manifested in children. The main objective of this project is to evaluate the prognostic relevance of selected markers (EWS/FLI-1, secondary genetic alterations, CD99, IGF-IR, NOVH, erbB-2 and TTF1) and the effectiveness of therapeutic approaches targeting some of these molecules. Another major goal of the project is the construction of ESFT c-DNA microarrays and tissue arrays, which will be used for the analysis of different histological subtypes of ESFT, primary and metastatic tumours and poor and good responders to chemotherapy. This will lead to:

- the definition of forthcoming risk-adapted strategies and targeted molecular treatments to be advantageously combined with established therapies;
- improved quality of life and survival for ESFT patients;
- prevention of risk in groups at risk.

Problem

The Ewing's sarcoma family of tumours (ESFT) includes: Ewing's sarcoma; primitive neuroectodermal tumour; Askin's tumour; paravertebral small-cell tumour; atypical Ewing's sarcoma. ESFT represents a peculiar entity in oncology. In spite of its absolute rarity (about 300-400 cases per year in Europe), ESFT is one of the most frequent solid neoplasm in paediatric age groups. Due to this fact, its impact on the health system is particularly important. The adoption of multimodal treatments with very aggressive chemotherapeutic regimens have significantly improved the chance of survival of ESFT non-metastatic patients, shifting the five-year survival rates to around 60%. Despite these important clinical results, which are usually difficult to obtain in rare diseases, several problems related to histogenesis, prognosis and treatment response are still open. In particular:

- the histogenesis of ESFT is still uncertain and the normal counterpart of ESFT cells is still unknown;
- the lack of prognostic factors obliges the use of non-differentiated treatments for all patients, leading to over-treatment of those patients who could benefit from less toxic therapies. The reduction of delayed side-effects is particularly important in this disease considering the young age of the patient and their long life expectancy;
- in the current state of ESFT treatment there is a survival 'plateau' (around 60% for patients with localised disease and 25% for highrisk groups) due to the lack of new drugs and toxicity that impedes more intense use of existing drugs. The identification of new targets for innovative therapeutic strategies is, therefore, strongly needed for this tumour. Progress is generally hampered by the rarity of the disease (in Europe about 400 cases/year) implying a limited number of cases for effective research. Moreover, because ESFT is an orphan disease, no private company will develop new therapeutic tools and take on the costs to conduct pre-clinical investigation.

Aim

The project will define prognostic markers and new therapeutic targets in the Ewing's sarcoma family of tumours (ESFT) through collaborative studies to provide rigorous scientific justification for the development of new therapeutic strategies for this rare disease, which is manifested for the most part in children. Goals expected to be achieved:

- with respect to the problem of toxicity, the project, by identifying the clinical relevance of a number of markers, may allow the differentiation of patients in terms of risk to recur. This will enable more aggressive treatments where these are justified, and avoid toxicity in cases where such treatments may be known to be unnecessary, with particularly significant consequences for the quality of life of the patients;
- successful treatment of therapy-resistant patients requires new strategies. Indeed, there is a desperate need for new therapeutic approaches in ESFT. A thorough study of the pre-clinical effectiveness of new targeted therapeutic strategies will be performed with the aim of the identification of the Achilles' heel in this disease and the consequent development of a tailored biological therapy to be used in association with conventional chemotherapy;
- by providing an organisational framework for collaboration the project will also allow multi-centre collection and analysis of cases as well as suitable collaborative research to allow genetic studies for the screening of high-risk patients and patients responding differently to chemotherapy.

Expected results

- The identification of prognostic factors in ESFT as a basis for the definition of individual therapeutic regimens, which would limit the incidence of acute side-effects and long-term morbidity as well as the economic and social consequences of intensive chemotherapy.
- The definition of patient selection criteria to be used as a basis for beginning a pivotal clinical trial.
- The creation of new therapeutic bullets against ESFT. They will be available at the end of the project as new drugs for ESFT treatment, together with the required toxicological

and pharmaco-kinetics studies. This is an important point because ESFT is an orphan disease and no private company will develop new therapeutic tools and take on the costs of conducting pre-clinical investigation.

- New therapeutic strategies for oncologists to increase the survival rate of ESFT patients through the pre-clinical evaluation of new drugs and strategies based on an immunological approach.
- New clues in the diagnosis and the screening of high-risk groups through the creation of an extensive tissue bank and the genetic profile analysis (cDNA microarray and tissue array analyses) of these samples.

Potential applications

Therefore the project, aiming to ameliorate treatment of ESFT, will have an impact on child health. In particular, the main objective of this project is to develop patient-oriented strategies for Ewing's sarcoma patients by:

- integrating different disciplines and advanced technologies to develop effective approaches or new tools for diagnosis, prognosis and treatment;
- elucidating the contribution of specific molecular and genetic factors to the histogenesis of the disease.

This work will unlock the potential of the individual studies carried out by each of the consortium partners, and it will define targeted therapeutic strategies of practical value in clinical settings and the clinical relevance of a number of markers that will allow the differentiation of patients in terms of risk of recurrence. It will also unlock the biological and clinical information potential behind multi-centre data collection and genetic analysis of patients, bringing basic knowledge to the application stage. Progress is generally hampered by the rarity of the disease, implying a limited number of cases for effective research. The creation of a multi-centre tissue bank and data collection will help to overcome a big obstacle. The application of new technology will be used to identify ESFT-related molecular mechanisms. The gene expression profile of ESFT will be analysed and new markers to be used for diagnostic, prognostic and therapeutic purposes will be identified.

The project made efforts in the integration of multi-disciplinary research capacities across Europe. The consortium includes pathologists, oncologists, immunologists, and molecular and cellular biologists. Moreover, PROTHETS lays emphasis on collaboration with small and mediumsized enterprises (SMEs), devoted to the development of specific tools for prognostic and therapeutic applications.

Finally, the development of evidence-based guidelines will ensure that the knowledge held and developed by and within the project will be distributed as widely as possible to have the highest possible impact on the biomedical world. Specified actions of the project are devoted to dissemination activities to ameliorate harmonious relations between cancer researchers and society, with particular regard to patient associations.

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Instrument
STREP

Project website
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Keywords | Neoplasm | stroma | angiogenesis | selective targeting | combination therapy | antibody | small molecules | oncofetal antigens | tumour neovasculature |

STROMA

Selective targeting of angiogenesis and of tumour stroma

Summary

Targeted delivery of therapeutic agents to the tumour microenvironment is a novel avenue for cancer treatment towards the development of more efficacious and better-tolerated anticancer drugs.

This project aims to identify new molecular targets which are selectively expressed in tumour stroma and in the neo-vasculature of aggressive tumours and to develop new therapeutic strategies based on high affinity binding molecules capable of selective localisation in tumour stroma and/or vascular structures. An effort to move the most promising product(s) generated within this Integrated Project into clinical trials is the ultimate scope of the project.

Potential application is the pharmacological treatment of solid neoplasms, maintaining or improving the present percentage of respondents, survival, disease-free interval, with improved safety and a better quality of life.

Problem

The majority of pharmacological approaches for the treatment of solid tumours suffers from poor selectivity, thus limiting dose escalation (i.e., the doses of drug which are required to kill tumour cells cause unacceptable toxicities to normal tissues). The situation is made more dramatic by the fact that the majority of anticancer drugs accumulate preferentially in normal tissues rather than in neoplastic sites, due to the irregular vasculature and to the high interstitial pressure of solid tumours.

One avenue towards the development of more efficacious and better tolerated anti-cancer drugs relies on the targeted delivery of therapeutic agents to the tumour environment, thus sparing normal tissues. This experimental strategy requires a range of diverse experimental techniques, for the identification of targets, for the isolation of binding molecules, and for their conversion into imaging and therapeutic products. Our approach has the potential advantage that immunohistochemistry, imaging and biodistribution data provide information about the selectivity of the anticancer drugs at several stages of the drug development process, and allow a rational optimisation of the most promising lead compounds.

Aim

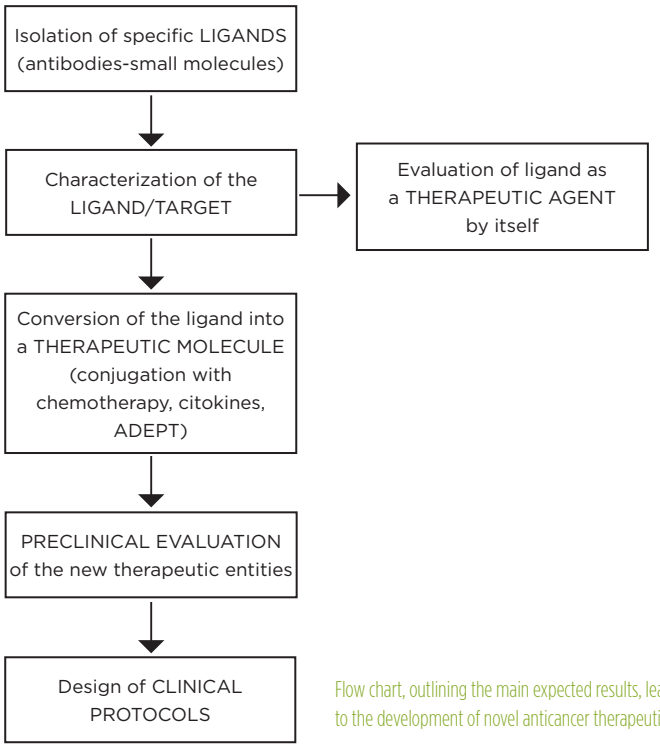
In the past, our consortium has developed innovative anti-cancer imaging and therapeutic strategies, based on recombinant antibody fragments, which have moved from the bench to the clinic. With the STROMA project, we plan to strengthen and extend the leading position of our European network in research and in the pharmaceutical development of ligand-based, targeted anticancer therapies, with a particular emphasis on the targeting of tumour neo-vasculature and tumour stroma.

This project focuses on the:

- identification and validation of molecular targets which are selectively expressed in the stroma and in neo-vascular sites of aggressive solid tumours. Endothelial cells and stromal cells are genetically more stable than tumour cells and can produce abundant markers, which are ideally suited for tumour targeting strategies;
- isolation of high-affinity binding molecules (small organic compounds, antibodies), which are specific for markers of angiogenesis and/or the tumour stroma, and are capable of selective localisation in the tumour environment, after intravenous administration;
- development of therapeutic strategies, based on specific binding molecules capable of selective localisation around tumour vascular structures and/or in the tumour stroma;
- dissemination of the research activities of the project.

Potential applications

We will consider the project as fully successful if at least one molecule enters clinical development for pharmacological treatment of solid neoplasms, maintaning or improving the present percentage of respondents' survival, disease-free interval, with improved safety and better quality of life.



Flow chart, outlining the main expected results, leading from target identification to the development of novel anticancer therapeutics.

Project number
LSHC-CT-2003-503233

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€ 6 000 000

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52 months

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IP

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www.stromaproject.org

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Keywords | Genomics | cancer metastasis | gene expression | RNA interference | cell-based assays |

TRANSFOG

Translational and functional onco-genomics: from cancer-oriented genomic screenings to new diagnostic tools and improved cancer treatment

Summary

The TRANSFOG project aims at the systematic identification and functional characterisation of novel cancer genes with high potential diagnostic and therapeutic value in breast, colon and lung cancers. The TRANSFOG partners will bring together world recognised competences and resources to reach the following, integrated research objectives:

- identification of novel candidate cancer genes through cancer- oriented genomic screenings, using tumour tissues as well as cellular and animal models, to generate a prioritised panel of genes involved in breast, colon and lung cancer progression and metastasis;
- full-length cDNA collection of the identified candidates, and setup of systems for high-throughput *in vitro* and *in vivo* gene delivery;
- collection of retroviral expression plasmids encoding small interfering RNAs, for systematic downregulation of candidate genes;
- identification of new molecular targets for cancer therapy;
- proteomic analysis of signal transduction and protein-protein interaction, focussed on the candidate cancer genes, which will allow better dissection of aberrant cancer signalling pathways;
- validation of the diagnostic potential of the identified cancer genes towards the clinical use of diagnostic molecular signatures;
- generation of a shared informatics platform for data handling and gene functional annotation. This will significantly increase European competitiveness, provide a huge structuring effect on the ERA in the field of functional oncogenomics, and depict several new molecular targets for anticancer drug discovery and advanced cancer diagnosis.

Problem

While extensive analysis over the last two decades led to a deep insight into the control of cell proliferation and survival, and their alterations during cancer onset, much still remains to be clarified about the genetic lesions and alterations of cell signalling that lead to aberrant activation of invasive growth, cancer progression and metastasis. It should be also noted that, after completion of genome-sequencing projects for many organisms, genes with an unknown function represent over 70% of all genes. This suggests that current comprehension of most biological and pathological processes is still very incomplete, particularly in the case of cancer progression, where systematic exploration of gene function is likely to yield a huge amount of information in the next few years. In this perspective, a crucial issue is the development of technologies for high-throughput functional analysis. Development of large-scale functional screens focused on cancer progression will require a coordinated approach involving complementary competences and establishment of dedicated facilities, for which TRANSFOG intends to provide an optimal organisational and financial framework.

Aim

The five key objectives of the TRANSFOG project are:

- Identification of novel cancer-related genes of high clinical-diagnostic potential, with a specific focus on progression and metastasis of colon, breast and lung cancers. This will be achieved mainly through extensive gene expression profiling of tumour/metastasis samples and of cell-based models of cancer progression. To extend the exploration range, differential proteomics and epigenetic analysis are also planned. The foreseen outcome is a ranked list of novel candidate cancer genes emerging from integration of the screening results, which will undergo functional characterisation and/or diagnostic validation.

- Set-up of technologies for systematic cancer gene functional analysis and for identification of new molecular targets. Gene functional analysis will be enabled by assembling collections of full-length cDNAs and of short interfering RNAs (siRNAs), subcloned in expression plasmids to assess the consequences of gene gain- or loss-of-function in cell-based and preclinical models.

- Systematic exploration of oncogenic/antioncogenic signalling pathways, epigenetic regulatory mechanisms. Taking advantage of the FL-cDNA and siRNA collections made available by the project, cellbased experimental systems to study protein-protein interaction, reporter gene expression and epigenetic modifications will be exploited for systematic analysis of the candidate genes. This will result in datasets of protein-protein interaction, transcriptional and epigenetic regulation allowing a comprehensive overview of the alterations in signalling and regulatory networks involved in cancer progression.

- Development of tools for diagnostic validation of molecular signatures for cancers of high population impact, namely of the colon, breast and lung. This will enable translation into clinical use of signatures obtained through the cancer-oriented genomic screenings performed by the participating units. In particular, the project is expected to define and validate prognostic signatures associated with the tendency of the above-mentioned cancers to give rise to metastasis.

- Establishment of a shared bioinformatic platform for functional oncogenomics data handling and standardisation. This will require a concerted effort towards codification of the various biological assays according to specific functional features analysed by each assay, using for example the Gene Ontology as a template (www.geneontology.org), and the sharing of analysis software and tools. Towards the same aim, a web-accessible platform based on the Distributed Annotation System (www.biodas.org) will be implemented.

Expected results

The project will go through three main phases:

Phase I (year 1): Initial set-up of experimental procedures for systematic cancer gene functional analysis and clinical validation; establishment of standards and tools for HTP data sharing and mining.

Phase II (years 2-3): Scaled-up, high-throughput gene functional analysis and clinical diagnostic validation of new cancer molecular signatures, and identification of new molecular targets for innovative cancer therapy.

Phase III (year 4): Final collection of results, dissemination of technologies and deliverables to the European cancer research community and cancer hospitals. Exploitation of the achieved results, mainly as new cancer diagnosis tools and the screening of new targets for cancer drug discovery.

The TRANSFOG project will deliver a consistent and integrated amount of functional data on genes of, as yet, unknown activity and biological role. In the process of reaching this objective, the participating units will be enabled to set up truly post-genomic efforts toward systematic gene functional characterisation. New technologies will be developed that will allow exploration of gene regulatory networks, protein- protein interactions and high-throughput cell-based evaluation of basic biological functions, such as motility, growth, apoptosis, invasion, adhesion, polarisation and more complex processes, as *in vitro* epithelial morphogenesis and angiogenesis. The technologies for systematic gene functional characterisation developed here will be useful for functional studies involving a variety of physiological and pathological processes, and will be made available to the scientific community in the frame of a collaborative research network. The bioinformatic networking endowed with the project will enable participating units to share tools for data handling, database exploration and functional gene annotation. It will also facilitate integration of the present network with other EC-funded networks and with the European and global post-genomic community.

Potential applications

A crucial issue in genomics is to develop enabling technologies. TRANSFOG will tackle this issue by developing:
- tools and standards for genomic data sharing, which will allow the results of cancer-oriented genomic screenings carried out by the consortium to be merged or made available in databases, thus generating a prioritised list of candidate cancer genes;
- plasmid collections carrying FL-cDNAs or siRNAs to achieve gainor loss-of-functions of the identified candidates.

Within a few years, competitive research will rely on the availability of genome-wide collections enabling systematic gene gain- or lossof- function and protein-protein interaction studies. Similarly, only high-throughput biochemical and biological assays will take full advantage of such collections, together with bioinformatic resources to handle and mine the data. A great advantage of a smaller collection focused on cancer gene discovery, like the one proposed here, is that it will enable functional analysis at a mid-throughput level, with a higher probability of success in the timeframe of the project. The know-how developed in the process of generating and employing such a collection will provide the basis for competitive, larger-scale studies to be carried out later on at the European level.

The willingness to understand and cure cancer will be the driving force for generating functional genomic technologies specifically aimed at improving management of the oncological patient. Indeed, a more precise evaluation of the tendency of a tumour to give rise to metastases will have a great social impact, particularly in helping reduce mortality and, at the same time, reducing overtreatment of patients that would not require aggressive anticancer therapy, and promoting direct, early exploration of alternative therapeutic strategies in patients with diagnostic signatures that predict poor prognosis.

Project number
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EC contribution
€ 6 000 000

Duration
54 months

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01/06/2004

Instrument
IP

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Treatment

Two major problems when treating cancer patients are the enormous complexity of the disease (and side-effects such as cachexia) and small therapeutic window when using classical cytotoxic drug regimens, resulting in serious toxicity and a strong reduction in the quality of a patient's life.
Depending on the particular type of cancer from which a patient is suffering, the standard treatments, comprise classical treatment such as surgery, chemotherapy, radiotherapy and combinations thereof. Innovative, so-called *targeted therapies* that aim specifically at cancer or the host's stroma cells and the processes involved in their survival and metastasis to other parts of the body are urgently needed since most cancers – unfortunately – find ways to resist the often aspecific treatment conditions and eventually kill the patient. For several cancers it has been convincingly demonstrated that patient survival rates under such conditions can hardly be improved if at all.
The 29 projects in this section address novel means of hitting cancer cells through collaborative research on new delivery and viral technology; by harnessing and optimising anti-cancer responses of the innate and adaptive immune system through the development of specific antibodies and vaccines that induce cell death or suppress critical signal transduction pathways that cancer cells need for survival and expansion, as demonstrated for the first time by Gleevec in chronic myeloid leukemia; by dissecting molecular mechanisms in cancer cells that allow resistance to chemotherapy; by developing imaging probes and devices that allow routine visualisation of selective drugs hitting their targets in a clinical setting; by developing treatment biomarkers based on gene expression profiles, differential cellular or molecular information obtained from different sources and by different technologies; and finally, by clinically validating personalised medicine approaches based on large patient cohorts.

Jan van de Loo

Keywords | Gene therapy | non-viral gene therapy | dermatology | biomedical engineering | electropermeabilisation | electroporation | DNA electrotransfer | antiangiogenesis | cancer treatment | new therapies | electric pulses | skin diseases | naked DNA | medical instrumentation |

ANGIOSKIN

DNA Electrotransfer of Plasmids Coding for Antiangiogenic Factors as a Proof of Principle of Non-Viral Gene Therapy for the Treatment of Skin Disease

Summary

The Angioskin consortium wants to bring the proof of concept that therapeutic genes can be safely delivered to skin by DNA electrotransfer (electrogenetherapy) in order to prevent or to treat acquired or inherited skin diseases. The Angioskin proposal is based on the results of the Fifth Framework Programme's (FP5) Cliniporator project (the analysis of the mechanisms of DNA electrotransfer and elaboration of a CE labelled pulse generator) and of the FP5's ESOPE project (the preparation of the standard operating procedures of Electrogenetherapy, electrotransferring a reporter gene in humans), and on a gene coding for a potent human antiangiogenic factor. This factor specifically binds to the αvβ3 and α5β1 integrins involved in angiogenic processes.

Problem

Non-viral gene transfer for the treatment of acquired or inherited skin diseases.

Aim

- To electrotransfer proprietary therapeutic antiangiogenesis genes to cutaneous metastases in humans, using the procedures validated in the ESOPE project, to show its clinical efficacy; non-invasive biophysical methods will be used to monitor the antiangiogenic effects.
- To develop new specific electrodes for the treatment of skin lesions.
- To validate the electrodes (safety, efficacy) on normal skin in animals, and analyse the effects of the electrotransfer of the antiangiogenetic factor on models of skin disease related to excessive angiogenesis, using non-invasive biophysical as well as histological methods to follow changes in the vascularisation of the lesion.
- Finally, to electrotransfer the therapeutic gene to a benign lesion in humans as a proof of concept of the use of non-viral gene therapy to treat acquired or inherited skin diseases.

Expected results

Electrodes, pulse generators, procedures, proof of concept of a new therapeutic approach, clinical validation of an antiangiogenic factor.

Potential applications

- Research
- Biotechnologies
- Medicine

Project number
LSHB-CT-2005-512127

EC contribution
€ 2 780 683

Duration
48 months

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Instrument
STREP

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Keywords | Angiogenesis | cancer | ocular disease | arthritis | PlGF |

ANGIOSTOP

Novel Anti-angiogenic treatment for Cancer, Arthritis and Ocular Neovascularization based on Inhibition of Placental Growth Factor (PlGF)

Summary

ANGIOSTOP proposes an approach to develop a new, safer and more effective anti-angiogenic medicine that reduces the pathological blood vessel formation associated with solid tumor growth, ocular neovascularization (diabetic retinopathy and macular degeneration) and rheumatoid arthritis. The proposed drug target is Placental Growth Factor (PlGF) and the candidate drug is a humanized neutralizing monoclonal antibody. This drug target selection is based on recent basic research on the role of PlGF in pathological angiogenesis and 'translational research' that established proof of concept in experimental animal models. Using a lead candidate anti-PlGF antibody, it has been demonstrated that inhibition of PlGF reduces solid tumour growth, inhibits ocular neovascularization and alleviates arthritis symptoms. ANGIOSTOP will assure the development of an anti-PlGF antibody that may constitute a new, safer and efficacious medicine for the treatment of diseases that depend on PlGF driven angiogenesis such as cancer, ocular disease and arthritis.

Problem

Most anti-angiogenic strategies are focused on blocking the interaction between VEGF and its receptor VEGFR-2. Despite the success of Avastin, it is unlikely that VEGF-inhibitors alone will be sufficient to halt tumour angiogenesis. Firstly, an increasing number of studies document that blocking the VEGF pathway leads to the induction of alternative angiogenic signals. Secondly, it has been reported that treatment of cancer patients with Avastin significantly upregulates the levels of PlGF. Finally, the currently available angiogenesis inhibitors have serious side effects thus mandating the development of additional angiogenesis inhibitors. Due to the potential application of angiogenesis inhibitors in disorders other than cancer, where the treatment is expected to start at earlier times after the disease onset and continue for longer periods, safer anti-angiogenic drugs without the risk of serious side effects are needed. By gene targeting study in mice, it has been shown that loss of PlGF does not cause any vascular defect during development, reproduction or normal adult life, while it severely impairs angiogenesis and arteriogenesis during pathological conditions including ischemia, inflammation and cancer therefore indicating that the ANGIOSTOP anti-angiogenic strategy targeting PlGF could represent a safer and more effective approach.

Aim

ANGIOSTOP aims to elaborate a comprehensive approach to the accelerated development of new efficacious and safer anti-angiogenic medicines that reduce the pathological blood vessel growth and can be used for the treatment of major progressive disorders such as cancer, ocular neovascularization (as observed in diabetic retinopathy and age-related macular degeneration) and arthritis. The overall objective of ANGIOSTOP is to develop an anti-PlGF monoclonal antibody. The roadmap comprises 'translational research' to validate previous proof of concept studies in new therapeutically relevant small animal models, both in terms of safety and efficacy, to evaluate PlGF expression and its possible upregulation in cancer patients, and to develop an industrial production process at the GMP level for critical path development.

We aim to perform extensive validation studies of our drug candidate to reduce the risk of failure as the drug advances into clinical trials and to manufacture this product for clinical trials. The ultimate goal of ANGIOSTOP is to develop an anti-PlGF monoclonal antibody for the safe and effective treatment of cancer, ocular disease and arthritis. The research will focus on a selected drug candidate but the new models and strategies will be of more general utility for the development of new medicines aimed at increasing or reducing blood vessel formation as well as for the advancement of our understanding of pathologic angiogenesis.

Expected results

- A lead humanized anti-PlGF antibody will be validated in appropriate animal models.
- Toxicology studies will identify a safe clinical dose and document the cross-reactivity profile and any toxic effects of the lead candidate antibody.
- Process development and industrial GMP manufacturing of the lead candidate antibody for critical path development will be carried out.
- The protein expression of PlGF will be examined in patient tumour samples. If PlGF levels correlate with certain tumour types and associate with grade and prognosis, such information may be beneficial for identification of appropriate patients groups.
- Development of a fully human back-up antibody with a similar or better pharmacological profile as compared to the lead candidate antibody will be performed for contingency purposes.

Potential applications

ANGIOSTOP has both strategic and specific deliverables and milestones. The new animal models and acquired knowledge on pathologic and therapeutic angiogenesis will transcend the specific aims of the drug development programs and be of strategic significance for angiogenesis research in general. The translational and critical path research program has a clearly defined ultimate deliverable: a new medicine based on PlGF-neutralizing antibody for anti-angiogenic treatment of certain solid tumours, ocular diseases and arthritis.

Project number
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Duration
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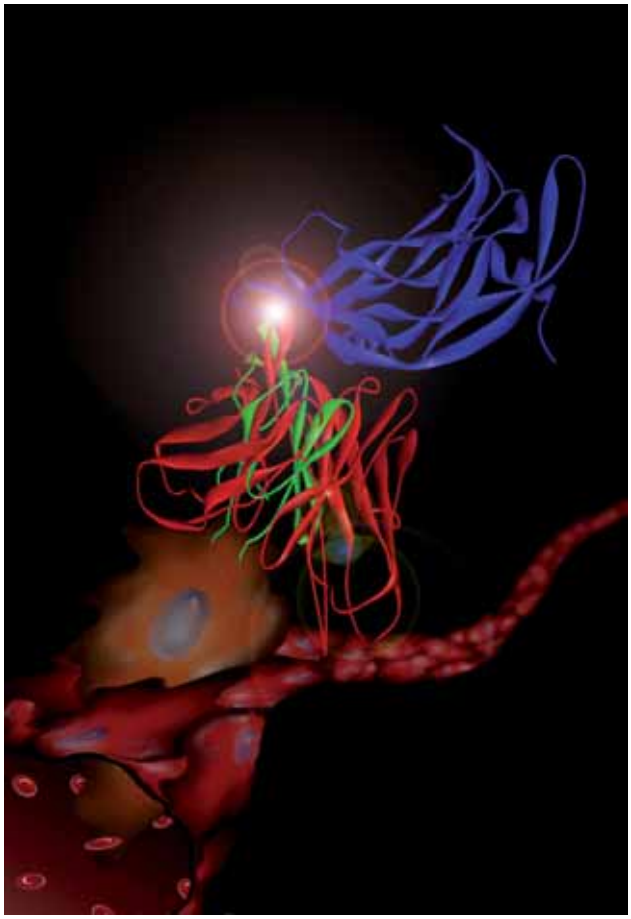
01/06/2006

Instrument
SME-STREP



ANGIOSTOP is exploring the therapeutic potential and pleiotropic mechanism of anti-PlGF, antibodies against placental growth factor (PlGF), a VEGF homologue, which regulates the angiogenic switch in disease but not in health. Anti-PlGF antibodies inhibit tumour growth by blocking angiogenesis. Distinct from VEGF inhibitors, however, targeting PlGF has been found to prevent infiltration of angiogenic macrophages, and thus do not switch on the angiogenic rescue program responsible for resistance to VEGF inhibitors. This mechanism is illustrated with anti-PlGF (depicted in blue) preventing PlGF (green) binding to its receptor VEGFR-1+ (red) expressed on macrophages (orange).

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Keywords | Cancer | gene therapy | signalling | apoptosis | CD40 | phosphoinositide 3-kinase | metastasis |

Apotherapy

CD40 ligand-based modalities for the treatment of cancer

Summary

Cancer is a major disease according to the WHO Mortality Data base (2004) and is responsible for approximately 25% of all deaths in the European Union. Epithelial tumours, such as those of the ovary, lung and oesophagus, have particularly poor prognosis, with only a minority of patients achieving a five-year survival. Conventional treatments, including chemotherapy and radiotherapy, have limited efficacy and frequently cause severe side-effects in patients.

The *Apotherapy* project brings together expertise from academic and biotechnology sectors across seven European countries with the aim of developing and validating novel anti-cancer agents with a wide therapeutic index and minimal side-effects. The focal point of our research is the utilisation of combined approaches which attack the tumour cell at multiple levels, achieving maximal apoptosis while limiting the risk of drug resistance. These approaches involve the efficient delivery of a pro-apoptotic molecule to cancer cells in combination with inhibitors of anti-apoptotic signal transduction pathways.

Specifically, the project will formulate therapeutic strategies which exploit the ability of CD40 ligand (CD40L), a TNF family member, to reduce proliferation, promote apoptosis and activate anti-tumour immune responses selectively in cancer cells. *Apotherapy* will develop state-of-the-art vehicles for the efficient delivery of CD40L to cancer cells, such as CD40L-encapsulated liposome formulations and recombinant adenoviruses expressing CD40L, and examine their *in vitro* and *in vivo* effects on tumour cell growth and metastasis.

Apoptosis induced by CD40 engagement is dramatically augmented in the presence of inhibitors of the phosphoinositide 3-kinase (PI3 kinase) pathway, which is frequently found activated in human tumours. The *Apotherapy* project will expand on the development of novel PI3 kinase antagonists and evaluate their *in vitro* and *in vivo* capacity to kill tumour cells and to amplify the CD40L-mediated effects on carcinoma cell growth, angiogenesis and metastasis.

Problem

Cancer has a major health, social and financial impact on Europe and its people. Current treatments include primary tumour resection and/or aggressive chemotherapy and radiotherapy in order to achieve both local control and effective therapy for distant metastases. Despite improved therapeutic regimens, mortality rates are still high. Moreover, the frequency of cancer incidence is predicted to increase and, as a result, its social and economic toll may reach even higher levels in the next decades. The growing cancer burden in Europe underscores the need to develop more efficient anti-tumour agents with a view to increasing survival and improving the quality of life of cancer sufferers.

Aim

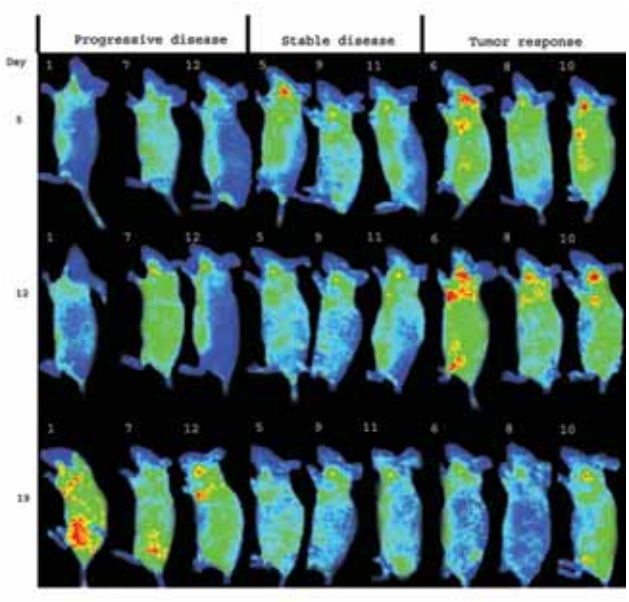
Apotherapy aims to combat cancer through an innovative combination strategy which targets cancer cells at multiple levels. One arm of this strategy is to encourage carcinoma cell apoptosis and immune recognition through the optimal activation of the CD40 pathway and the other is to suppress tumour cell survival mediated by the PI3 kinase signaling pathway. This strategy has been designed to achieve maximal inhibition of tumour growth while limiting the risk of side-effects.

Expected results

- The *Apotherapy* project will provide new information about targeting the CD40 and PI3 kinase pathways in solid tumours.
- The project will develop and evaluate viral and non-viral vectors for the efficient and tumour-specific delivery of anti-cancer agents *in vivo.*
- *Apotherapy* will characterise novel antagonists and inhibitors of the anti-apoptotic PI3 kinase signalling pathway.
- An extensive pre-clinical evaluation of CD40L delivery systems in combination with PI3 kinase pathway antagonists will be performed, aided by *in vivo* imaging technology.

Potential applications

The *Apotherapy* project will lead to the development of novel anti-cancer strategies which will be directly applicable to the clinic for the benefit of cancer sufferers. The strong focus on translational research will translate R&D results into tangible benefits for health, science and economy in Europe.



Green-fluorescence protein- expressing lung tumours in mice are visualised by *in vivo* imaging. This technology is used to monitor tumour growth following treatment with recombinant adenoviruses.

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LSHC-CT 2006-037344

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Instrument
STREP

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apotherapy.med.uoc.gr

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ATTACK

Adoptive engineered T-cell Targeting to Activate Cancer Killing

Summary

Each year in the EU millions of people are diagnosed with cancer and there are over one million deaths from the disease. Thus research into improved treatments is critical and immunotherapy research, focusing on the power of the immune system, is one important new approach to treatment. The ATTACK Project is based on the development of genetically engineered T cells to target cancer. The strategies that produce engineered T cells employ the transfer of tumour targeting receptors on the outside surface of the T cells using viral vectors to help the T cells to bypass the mechanisms of immune controls triggered by the tumour. Whilst the project addresses the scientific basis behind this technology it has clear clinical objectives for the future.

Problem

Cancer is an increasing problem within the EU, and as it is predominantly a disease of old age this will continue to increase as the population ages. Despite significant progress in the fields of early diagnosis and standard treatments including radiotherapy and chemotherapy, the outlook for most metastatic cancers remains bleak. In view of this, novel treatment approaches are being actively investigated.

Aim

ATTACK aims to improve engineered T-cell function and to perform pre-clinical studies which will underpin future clinical trials. With this in mind, ATTACK will also enhance the understanding of the mechanisms involved in tumour evasion of immune control.

The overall objectives are broken down within six work packages (WP):

- optimisation of two receptor-based strategies to endow the T-cells with tumour specificity (WP1 and 2). The first strategy is based in engineering T-cells to express recombinant T-cell receptors complex (TCRα and β) recognising MHC restricted antigens at the surface of the tumour cells (WP1). The other strategy is based on chimeric immune receptors (CIR), which are scFv or small antibody molecules linked to the TCRζ (WP2);
- compare the *in vivo* efficacy of the redirected T-cells in physiologically relevant animal models (WP3). This will include examining the mechanisms of action of the T-cells and improving their efficacy;
- enhance cytotoxicity, proliferation, survival, tumour homing or other features to increase anti-neoplastic activity and safety of engineered T-cells for current and future applications in T-cell therapy trials (WP4);
- improve protocols for T-cell selection, expansion and transduction (WP5);
- looking into safety of the improved T-cells in mouse models for future clinical trials in patients (WP6).

Expected results

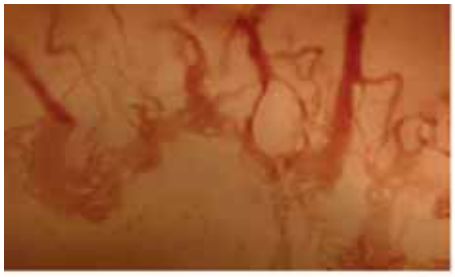
The project started in November 2005 and so far a website has been created for the dissemination of information within a secure portal for the members of the ATTACK project and external pages for dissemination to the general public.

The next five years will bring different sets of results established in tumour cell lines and in mouse models as well as a variety of genetic and molecular data testing performance and specificity of the two engineered T-cell strategies.

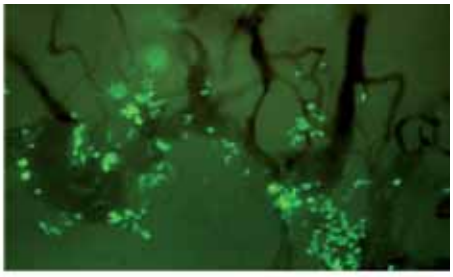
- Animal models will give important clues on the fundamental mechanisms of action of the engineered T-cells and the immune response they trigger. Mouse models will allow comparison of relative efficacy of T-cells redirected with scFv and TCR specific for the same antigen.
- Animal studies will also enable the testing of different protocols aimed at improving the engineered T-cell killing function employing chemokines or cytokines that can be applied to the clinic later. State-of-the-art imaging technology, like the dorsal skin fold window chamber, will be used to follow migration of the engineered T-cells *in vivo* and in real time experiments.
- The development and testing of various products from the commercial partners will define unique protocols for the selection and expansion of engineered T-cells.
- Finally important safety data on auto-immunity, immune response against the different parts of the receptor introduced in engineered T-cells will be collected from the *in vivo* experiments in order to gather pre-clinical data indispensable for future clinical trials.
- Read outs from these results will be in peer-review publications, popular articles and other published material such as poster presentation at international meetings.

Potential applications

- Early phase clinical trials.
- Promote and enhance discussions with national ethical bodies to understand and facilitate gene therapy trials with further pre-clinical data arisen from the ATTACK project.



TUMOR VASCULATURE: 10X



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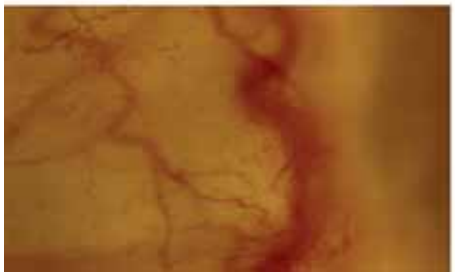
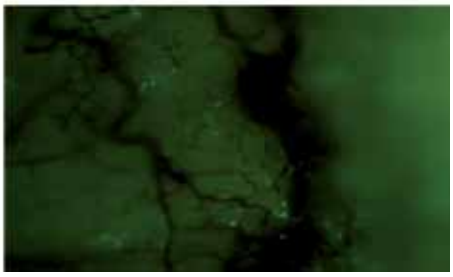


NON-TUMOR VASCULATURE: 20X



NON-TUMOR VASCULATURE: 20X

T cells engineered to recognise a melanoma antigen and expressing Green Fluorescent Protein. The engineered T cells accumulate in tumor vasculature but not in non-tumor vasculature after T cell transfer. Real-time images were taken immediately after T cell transfer using an intravital fluorescence microscope. (R Debets, Erasmus MC).

Project number
LSHC-CT-2005-018914

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€ 11 981 087

Duration
60 months

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Instrument
IP

Project website
www.attack-cancer.org

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Keywords | Baculovirus | gene delivery | insect cells | vertebrate cells | adeno-associated virus (AAV) | prostate cancer | age-related macular degeneration (AMD) | muscular disorders (MD) |

BACULOGENES

Use of baculovirus as a vector for gene therapy

Summary

Gene therapy is a technique to deliver therapeutic nucleic acids into somatic cells and is one of the most promising therapeutic methods under development for treating a large scope of pathologies, ranging from genetic disorders (e.g. myopathies) to degeneration syndromes or cancers. The potential of gene therapy is still not fully exploited mainly because of significant limitations related to the safety, gene delivery capacities and some other properties of the currently used vectors. Baculoviruses (BVs) are insect pathogenic DNA viruses and are not known to replicate in mammalian cells giving them an advantage in terms of safety over classical mammalian viruses currently used as vectors such as adeno-associated virus (AAV), adenovirus, murine retroviruses and lentiviruses. The most promising baculovirus for gene therapy is the well known *Autographa californica* multiple nucleopolyhedrovirus (AcMNPV). It is inherently safe and can deliver large pieces of DNA on its genome (≥50 Kbp). BV replication and virus production does not occur in mammalian cells and BV is not known to be associated with any human disease. However, by using a vertebrate active expression cassette as a part of baculovirus genome, efficient gene expression can also be directed in non-target cells. A large range of vertebrate cells has been shown to be permissive for AcMNPV transduction *in vitro* and *in vivo.* BV technology has been used for years for producing recombinant proteins and thus large scale production technology is readily adaptable for the exploitation of gene therapy approaches. In addition, BV vectors can be used efficiently for producing other gene therapy vectors such as AAVs. The BV genome is well-known and several selective targeting approaches engineered into the virus envelope and capsid have been developed. The BACULOGENES project aims to develop clinically suitable methods for the development, production, testing and validation of next generation stabilised and selective BV vectors for gene therapy applications as well as to optimize production of new AAV serotype vectors. Target diseases for *in vivo* gene delivery with selectively targeted BV include muscle disorders, age-related macular degeneration and prostate cancer. The BACULOGENES consortium consists of 8 partners from 6 countries, including pioneers in the use of BVs for mammalian gene transfer applications and 2 major established gene therapy vector producing companies in EU. The consortium will devote its efforts not only to BV gene therapy applications, but also to the development of large scale production, downstream processing, purification and analysis methods. The quality control and validation assays, and all issues related to regulatory aspects required for the clinical exploitation of BV technology will be covered.

Problem

Validation of BV as a vector for gene therapy and AAV production implies meeting several challenges including solving production issues. In fact, the use of BVs to be used as new efficient and adapted vectors for gene therapy fully lies on the demonstration of their ability to:

- carry large and/or multiple genes;
- exclusively target selected tissues;
- deliver the therapeutic gene with a high efficiency;
- generate an acceptable immunological and toxicological response;
- show high stability;
- be able to be produced and purified in large quantities. The BACULOGENES project precisely addresses these issues.

Aim

The innovative strategy of BACULOGENES relies on the original engineering of BVs (AcMNPV) to make them safe, specific and efficient vectors for gene therapy. BACULOGENES approach consists in stabilizing the BV genome through deletion and insertion of specific sequences in combination with transgenes relevant to the disease targeted.

The 'stabilized' BVs will then be engineered to:

- enhance the capacity to deliver the therapeutic gene(s) to the right cells;
- optimize the therapeutic gene expression in the right cells;
- make BVs less immunogenic and potentially invisible for the immune system (stealth virus).

Such improvements of the BV will be obtained through envelope protein, capsid and genome modifications. In parallel, the baculovirus expression system will be optimized for the production of different serotypes of AAV by using stabilized constructs. In addition, the development of baculovirus constructs allowing the production of recombinant AAV without the concomitant production of baculovirus is planned.

Project number
LHSB-CT-2006-037541

EC contribution
€ 2 499 746

Duration
36 months

Starting date
01/01/2007

Instrument
STREP

Project website
under preparation

Expected results

The BACULOGENES project will strengthen the European leadership, knowledge and competitiveness in BV technology through the delivery of novel and validated efficient vectors and platform technology for the exploitation of potential clinical applications of gene therapy. This project will thus pave the way for the BVs to clinical applications, which has never been experimented as of yet and will provide an optimized BV based AAV platform for gene therapy purposes. The project will also provide the biotech community with a highly efficient manufacturing process and associated QC methods for BVs processing.

Potential applications

Optimized production platform for next generation baculoviruses have wide applications in gene delivery, protein production and virus particle generation.

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Keywords | Bioinformatics | pharmacology | grid technology | library design | *in-silico* prediction of drug-like properties | prediction of ADME parameters | predictive toxicology | creation of virtual libraries |

CancerGrid

Grid-aided computer system for rapid anti-cancer drug design

Summary

In the three years of this multidisciplinary research project, the 10-member Consortium plans to develop and refine methods for the enrichment of molecular libraries to facilitate discovery of potential anti-cancer agents. Using grid-aided computer technology, the likelihood of finding anti-cancer novel leads will substantially increase the translation of basic knowledge to application stage.

In particular, through the interaction with novel technologies and biology, the R&D consortium aims at:

- developing focused libraries with a high content of anti-cancer leads;
- building models for prediction of disease-related cytotoxicity and of kinase/HDAC/MMP and other enzyme (i.e. HSP90) inhibition or receptor antagonism using HTS results;
- developing a computer system based on grid technology, which helps to accelerate and automate the *in silico* design of libraries for drug discovery processes, and which is also suitable for future design of libraries for drug discovery processes that have different biological targets (the result is a new marketable technology).

Problem

After the completion of the sequencing stage of the human genome project, the major focus of discovery efforts turned to the identification of the druggable portion of the genome that is linked to pathological states and is able to interact with the drug-like chemical space, restoring normal functions.

Apparently, the druggable genome is a subset of the 30 000 genes in the human genome that express proteins and represent, in many ways, an unprecedented gift and exceptional opportunity for drug discovery scientists and for patients who are hoping for therapies of diseases currently uncured. That subset (estimated as ca. 3 000 proteins) is able to bind drug-like molecules as characterised by the Lipinski's rule-of-5 criteria.

In order to find more rapidly small molecule modulators to the newly emerging validated targets, the high-throughput screening provides a reasonable solution to screen large compound libraries. However, it seems most of the targets can be classified into large target families such as kinases and GPCRs: thus, development of target focused libraries could dramatically increase the hit rate as well as open the way to identifying selective inhibitors/antagonists within the target families.

The idea of 'focused libraries' or 'targeted libraries' of molecules emerged in recent years as a 'compromise', or as an attempt to bridge between two seemingly conflicting approaches to drug discovery:

- high Throughput Screening (HTS), by which hundreds of thousands of compounds, mainly in big pharma, were tested against a (hopefully validated) biological target such as a protein or a cellular system. The basic assumption of HTS is that large numbers and diversity should cover chemical space well enough to find, at least, 'hits' (that are active in micromolar concentrations) which may subsequently be transformed to 'leads' (with affinities in the nanomolar range and with reasonable drug-like properties) and finally to drug candidates. Combinatorial chemistry has also been on the side of HTS, presenting the ability to synthesise huge amounts of derivatives based on specific 'scaffolds';
- rational drug design approaches such as structure-based design and ligand-based design. The first takes into consideration the detailed atomic structure of the target and the possibilities for forming physical interactions (i.e., hydrogen bonds, Van der Waals interactions, electrostatic complementarity, hydrophobicity, etc.) between small molecules and specific sites on the targets, while the second depends more on properties of known active molecules and uses similarity ideas (including 'pharmacophore' searches) to discover new active molecules. The substantial reduction in discovering new chemical entities by big pharma in recent years has been in part attributed to the failures due to very low hit rate in both the HTS and Combichem, on the one hand, and on the inability to properly taking into account the pharmacokinetic (ADME/Tox) effects as well as entropy, solvation and target flexibility in structure- and ligand-based designs.

A landmark in introducing pharmacokinetic considerations to drug design and development has been the 'Rule of 5' of Lipinski. This idea, which is now less than a decade old, also provided an immediate tool to reduce the size of combinatorial libraries and of HTS candidates by 'filtering', i.e., requiring that all molecules must pass the Lipinski rule (three out of four conditions for the limiting of molecular weight, calculated lipophilicity, and the numbers of H-bond donors and acceptors) in order to be in the proper bioavailability range.

The molecules that passed the Lipinski filter were thus targeted on oral bioavailability, and their numbers were much smaller than those for the initially planned experiments. The idea of 'filters' thus gained momentum, and additional filters such as those of Veber (limiting the number of rotatable bonds and the size of polar surface area), also for bioavilability, were suggested. Both Lipinski and Veber rules did not consider directly any conformational aspects (3-dimensional

descriptors of the molecules to be tested, but pharmacophore searches (ligand-based design) and virtual docking and scoring (structure based design) serve as subsequent filtering processes in 3D that cover the 'affinity' part of drug action, while the other filters mostly deal with 'drug transport' issues.

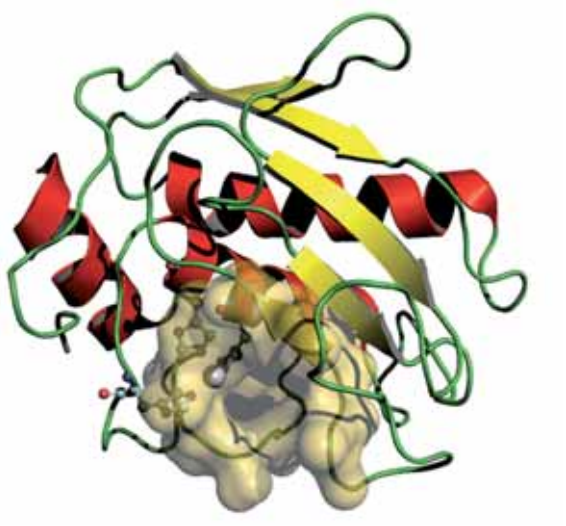
These two properties are, to a large extend, orthogonal. Thus, one may regard the filtering process as beginning with huge numbers of molecules, which are reduced to a smaller set by chemical descriptors. This smaller set may then be studied with more detailed conformations at the pharmacophore level, reducing it further to a group of molecules which may be docked virtually to the assumed target, finally leaving a small set of substantially 'focused' or 'targeted' lead candidates.

But, even that approach suffers from many drawbacks. Lipinski and Veber rules can not distinguish well between drugs and non-drugs, and are clearly not appropriate indicators of 'drug-likeness'. Neural networks have been applied specifically to this problem and managed to distinguish properly between drugs and non-drugs, but have the disadvantage of 'hidden layers' which do not enable to plan and design novel molecules.

A drug-like index has been suggested but is based on fragment identification and therefore limited in its ability to discover novel structures. Structure-based approaches can consider small molecule flexibility, but are still inappropriate for dealing with the flexibility of the protein targets, especially with the flexibility of backbone and of larger loops. The scorings in docking methods have recently been exposed to much criticism. Using single conformations in pharmacophore searches is clearly inappropriate, because it has been shown that small molecules bind to proteins in conformations that are higher in energy than their global minima. Toxicity predictions have not yet reached enough reliability to prevent major toxicity threats by drugs. The need for selectivity has not yet been properly addressed in the preparation of focused libraries.

Therefore, although many companies nowadays are offering focused libraries for kinases, GPCRs and other families of molecules, there is a great need to improve the production of such libraries in order to shorten the time for discovery and to save enormous expense. A main stumbling block on the way to solving such issues is the complex combinatorial nature of the problem of library construction and drug design.

In this proposal, we include methods that deal directly with the combinatorial nature of the problems, that have been shown to solve combinatorial problems in a highly satisfactory manner, that discover the global minimum in most cases and retain a large set of best results, many of them excellent alternatives to the global minimum.



Typical fold of matrix metalloproteinases structured in 3 α-helices (red) and 4 parallel and 1 antiparallel β-sheets (yellow). The binding site is represented by a white surface while the zinc ion is shown as a light-gray sphere and the three catalytic histidines are rendered as ball-and-stick.

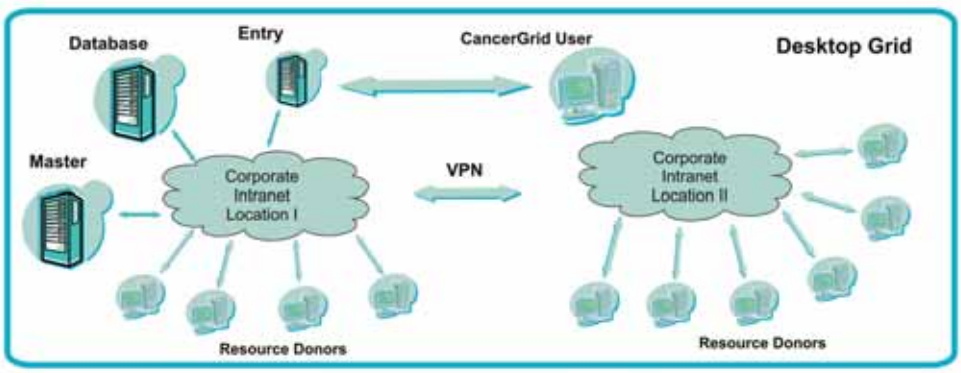
Expected results

Novelties and added values of the project:

- virtual focused libraries of anti-cancer agents;
- potential anti-cancer agents;
- HTS technology;
- data for model building purposes;
- models able to predict anti-cancer properties;
- CancerGrid System: a grid-based computer aided tool that able to provide anti-cancer candidates faster and in a more efficient way, also suitable to develop candidates for other targets.

Potential applications

The models developed within the framework of this project can be used for filtering large discovery libraries to find anti-cancer drug candidates, and to design anti-cancer focused libraries. The CancerGrid computer system will be able to support the design of lead compounds in general, not only in the anti-cancer field, but in any other activity area. Thanks to its grid-based architecture, the system will be able to predict molecular descriptors for compound libraries, containing a large number of molecular structures, in a short time. When calculating 3D molecular descriptors, the system will take all major conformers into account. This enables the calculation of information-rich molecular descriptors, and the development of reliable linear and non-linear models. The system will also be able to apply these models to predict the biological activity or chemical/physical property of the compounds.



Grid Based IT Support for Drug Discovery.

Project number
LSHC-CT-2006-037559

EC contribution
€ 2 804 075

Duration
36 months

Starting date
01/01/2007

Instrument
STREP – SME

Project website
www.cancergrid.eu

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Keywords | Therapeutic vaccine | immunomonitoring | DC | CTL | CD4 | Treg | melanoma | tumour escape | Ag processing |

CANCERIMMUNOTHERAPY

Cancer immunology and immunotherapy

Summary

The first part of the project consists of clinical trials of vaccination, to compare various vaccines, such as peptides and RNA, with different types of immunological adjuvants and dendritic cells. Safety and clinical efficacy will be the primary endpoints of these trials. A large effort will be devoted to monitoring the anti-vaccine T-cell responses, as examining the correlation between immunological and clinical responses to the vaccines will be crucial to understanding which factor(s) limit tumour regression. A second part of the project,tightly connected to the clinical trials as it uses biological material from the vaccinated patients, consists of optimising tumour vaccines and combating immune evasion. Foreseeable mechanisms of tumour escape will be analysed and correlated with the clinical results. Improved modalities of vaccination will be tested and new target antigens will be identified. All these results will help to design improved vaccines. Finally, considering the complexity of mechanisms that may lead to or prevent tumour regression in vaccinated patients, we propose to explore more fundamental aspects of the anti-tumour immune response. This includes the cross-presentation of tumour antigens by dendritic cells, recruitment of cells of the innate immune system, involvement of suppressor T-cells, and development of murine models of inducible tumours. If new concepts emerge from this work, they will also help in the design of better vaccines.

Problem

Cancer is a major life-threatening disease and the second greatest cause of mortality in Europe after cardio-vascular diseases. Classical cancer treatment still relies on surgery, chemotherapy and radiotherapy. Despite clear progress in some cancer types, cancer therapy in general often fails to prevent disease progression to metastatic disease. In addition, these approaches are by themselves very toxic, imposing a heavy burden of side effects on the patient. There is clearly a need for new therapeutic approaches that would be more efficient and less toxic.

Aim

The ultimate objective of this Integrated Project is to develop a therapeutic cancer vaccine with defined tumour antigens that would provide a clinical benefit in at least 40 % of patients. This threshold of 40% of vaccinated patients showing an objective tumour response, in the absence of unacceptable toxicity, would definitely qualify immunotherapy as a standard cancer treatment. Further improvements could come from refining the vaccinations, and from combining tumour vaccines with other modalities of cancer treatment.

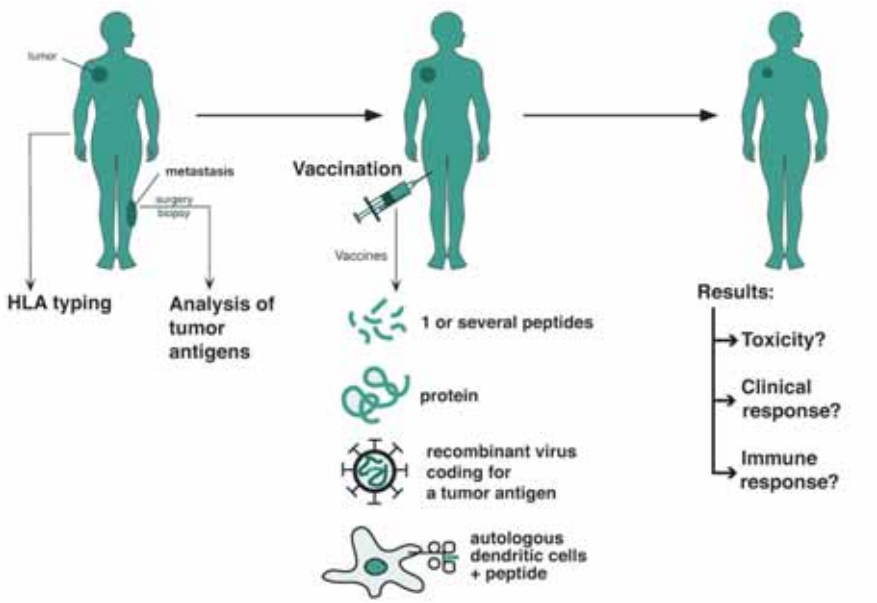
Expected results

We believe that the principal objective of our project is reachable, for the following reasons:

- the preliminary observation that vaccination with tumour antigens can be associated with tumour regressions, and in a few cases with sustained remissions, is encouraging, as it indicates that the vaccines tested so far have an anti-tumoural activity. Considering that vaccine-induced immune responses and tumour regressions seem to be correlated, and that the immune responses that have been detected so far appear to be quantitatively weak, it is reasonable to hypothesise that vaccines with a greater immunogenicity, such as those we plan to investigate, will also have a greater clinical efficacy;
- our project will build a close interaction between the research laboratory and the clinic, which allows new ideas emerging from observations made in either of these two fields to be integrated rapidly into new projects;
- our consortium comprises groups with an excellent record in clinical trials, T-cell immunology, dendritic cell biology, and mechanisms of tumour resistance. Many of these groups have a longstanding experience of collaborative programmes with each other, both in the laboratory and the clinical trial fields.

Potential applications

Development and validation of surrogate end-points is a high priority in cancer vaccine research. The project will contribute to this goal by promoting standardised assays and methods for the immunomonitoring of clinical trials. In practice, validation of these surrogate markers may prove extremely useful for meaningful comparisons of various immunisation modalities and as markers of consistency for a given product.



Cancer immunotherapy with defined tumor antigens:
antigens that have been identified as specifically expressed by the tumor cells are used in therapeutic vaccination trials to stimulate anti-tumor lymphocytes. Patients are monitored for signs of tumor regression and for the induction of anti-tumor immune responses.

Project number
LSHC-CT-2006-518234

EC contribution
€ 12 185 102

Duration
48 months

Starting date
01/03/2006

Instrument
IP

Project website
www.cancerimmunotherapy.eu

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Keywords | Cancer chemotherapy | drug resistance | toxicity | lung cancer | melanoma |

CHEMORES

Molecular mechanisms underlying chemotherapy resistance, therapeutic escape, efficacy and toxicity

Summary

The CHEMORES project aims to improve the outcome of cancer chemotherapy by developing novel tools to predict tumour response to treatment as well as individual toxicity to chemotherapy. The project will thus seek to identify and validate mechanisms of intrinsic and acquired chemotherapy resistance, as well as predictors of efficacy and of individual toxicity.

This is achieved by integrating the work of groups conducting large clinical trials with preclinical research groups, as well as with state-of-the-art platforms for genomic and proteomic analyses and bioinformatics. The participants have chosen to focus on melanoma and lung cancer as model tumours of separate histogenetic types exhibiting intrinsic resistance and/or a high degree of acquired resistance to chemotherapy.

Candidate mechanisms of drug resistance and therapeutic efficacy will be identified using genomic and proteomic analyses of sequential tumour samples and paired sera obtained before and after chemotherapy, as well as experimental systems, including *in vitro* studies of tumuor cell lines, transplanted human tumours and novel animal tumour models. These putative mechanisms will then be validated in further analyses of larger sets of tumour biopsies from patients. Functional studies of novel mechanisms and pathways will be also performed using *in vitro* systems and animal models. The result of these activities will thus be a set of clinically and functionally validated mechanisms of chemotherapy resistance and therapeutic efficacy.

Likewise, large-scale genomic analyses of patients receiving chemotherapy as part of clinical trials will be performed, in order to validate novel markers of individual toxicity following chemotherapy.

Problem

Resistance to systemic chemotherapy still remains one of the greatest problems in clinical oncology, and contributes to the death of a large number of cancer patients. Despite extensive efforts, no significant progress has been made in solving this fundamental problem during the last decades. Not only have efficient means to overcome chemotherapy resistance not been identified, but also the development of clinically useful tools to predict response to chemotherapy has been largely unsuccessful.

The different aspects of the chemoresistance problem are well illustrated in the two model tumours that will be studied. The two main subtypes of lung cancer are small cell lung cancer (SCLC) which is highly chemosensitive with response rates of 80% to chemotherapy; and non-small cell lung cancer (NSCLC) that is moderately chemosensitive with response rates of 30-60%. For all stages and types of lung cancer (NSCLC/SCLC), relapse after primary therapy is common, at which stage most patients have developed an acquired resistance to chemotherapy and seldom respond to second line treatment. In lung cancer, a therapeutic plateau has thus been reached with existing cytotoxic drugs and further improvements in survival are dependent on our understanding of the molecular mechanisms of chemoresistance.

There is no effective systemic therapy for metastatic melanoma and only a small minority of patients with melanoma respond to chemotherapy, which also has no discernible impact upon median overall survival. In the adjuvant setting interferon-alfa (IFN) is the only agent that has demonstrated a consistent effect on relapse-free survival, but without a significant impact on overall survival. We have as yet no tools to identify the patient population that benefits from treatment with IFN. Thus, improved knowledge regarding mechanisms of resistance is needed in order both to develop predictive tests and to modulate resistance and thus improve the therapeutic outcome in melanoma.

Cancer chemotherapy is frequently associated with severe toxic side-effects. Novel tools to identify individuals with an increased risk of developing severe side-effects are required in order to avoid such adverse events.

Aim

The overall aim of CHEMORES is to improve the outcome of cancer chemotherapy by developing novel tools to predict tumour response to treatment as well as individual toxicity to chemotherapy.

Expected results

The novel knowledge obtained through the project will lead to new tools for prediction of treatment outcome as well as toxicity of chemotherapy. This knowledge may also be used to identify and prepare for pre-clinical development of potential novel modulators of drug resistance based on validated mechanisms and pathways. The new information obtained in CHEMORES will be disseminated to the medical profession and other key stakeholders, such as health care providers, patient organisations and policy-makers.

Project number
LSHC-CT-2006-037665

EC contribution
€ 8 710 300

Duration
60 months

Starting date
01/02/2007

Instrument
IP

Project website
www.chemores.org

Potential applications

Predictive tests of response to chemotherapy may be used in medical oncology to select patients with an increased likelihood to benefit from therapy. The novel information on molecular mechanisms responsible for resistance to chemotherapy may lead to development of modulators of resistance. Both these advances may in turn lead to improved results of cancer chemotherapy. The development of tools to predict severe drug toxicity will lead to safer cancer chemotherapy.

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Keywords | Children | cancer | leukaemia | T lymphocytes | chimaeric T-cell receptor |

CHILDHOPE

Chimaeric T cells for the treatment of paediatric cancers

Summary

Leukaemias are the most common cancers affecting children while malignant lymphomas, including non-Hodgkin lymphomas (NHL), come in third position after brain tumours. A significant number of children with leukaemia/lymphomas still fail current therapies.

The aim of the CHILDHOPE project is to develop a safe and efficient adoptive immunotherapy for children with advanced or refractory malignancies. CHILDHOPE particularly focuses on three paediatric tumours: acute B-lineage lymphoblastic leukaemia, non-Hodgkin B-lineage lymphoma and acute myeloid leukaemia.

The CHILDHOPE project is a new approach in paediatric cancer treatment since it brings from bench to bedside (and back) an innovative technology as yet never applied in children with advanced or refractory haematopoietic malignancies.

The CHILDHOPE translational research project will focus on:

- improving and testing the efficacy and the safety of anti-leukaemia/lymphoma chimaeric T cells in relevant preclinical models *in vitro* and *in vivo* in mice;
- scaling-up this technology to numbers suitable for a clinical application in children with haematopoietic malignancies;
- based on biological material obtained from our preclinical models and from children treated with these genetically engineered T cells, dissecting the interface between the host's tumour and immune cells and using this knowledge to understand the mechanisms of anti-tumour action, validate novel targets and diagnostic tools specific to children affected with leukaemia or lymphomas.

The CHILDHOPE project is built on the excellence of a network of EU-based partners with a broad experience in the field of paediatric haematology and oncology, immunology and cell and gene therapies, and integrates the International Confederation of parents of children with cancer and an SME specialised in project management.

Problem

Intensification of post remission therapy and addition of autologous or allogeneic haematopoietic stem cell transplantation (HSCT) have marginally improved outcome in children with relapsed leukaemia or lymphoma. Failure to induce prolonged remissions in a large portion of relapsed children, and the toxicity of current regimens in this age category with unique physiological parameters, has led to a resurgence of interest in immunotherapies.

Administration of tumour-specific T cells (adoptive immunotherapy) has proven to be an effective cancer treatment: allogeneic HSCT and donor-leukocyte infusion (DLI) can induce lasting remissions in patients, including children, with a range of malignancies; and Epstein-Barr virus (EBV)-specific T cells can cure patients with post-transplant lymphoproliferative disorder (PTLD). However, considerable barriers hinder wider application of this promising form of immunotherapy. It is difficult and often impossible to select and expand tumour-specific T cells or, in an allogeneic setting, to separate T cells causing graft-versus-host disease (GVHD) from tumour-reactive ones. Further, tumour cells often lack inflammatory cues and the appropriate environment to maintain a persistent immunological rejection. Absence of a specific means of destroying adoptively transferred T cells in the face of unacceptable toxicity has also stalled clinical studies.

Many of these barriers can be now overcome by *ex vivo* genetic engineering of T cells using gene-transfer technology, thanks to pioneering work performed by us and others in the last decade. Initially cumbersome and impractical, this technology has matured to the point of effective clinical application. However little is known about the homing and function of the different subsets of tumour-specific T cells once re-injected in patients. Dissecting the killing mechanisms of these tumour-specific T cells – especially once they have been administered *in vivo* in children – and elucidating some of the reasons for their failure in certain patients will ultimately improve our knowledge of the host-tumour interface and help design enhanced strategies using engineered T cells against paediatric and adult cancers.

Aim

The CHILDHOPE project builds on the excellence of a network of EU-based partners with broad experience in the field of paediatric haematology and oncology, immunology and cell and gene therapies. The CHILDHOPE project is unique since it brings from bench to bedside (and back) an innovative technology as yet never applied in children with advanced or refractory haematopoietic malignancies. The CHILDHOPE translational research project will focus on:

- improving and testing efficacy and the safety of anti-leukaemia/lymphoma chimaeric T cells in relevant pre-clinical models *in vitro* and *in vivo* in mice;
- scaling-up this technology to numbers suitable for a clinical application in children with haematopoietic malignancies;
- based on biological material obtained from our preclinical models and from children treated with these genetically engineered T cells, dissecting the interface between the host's tumour and immune cells and using this knowledge to understand the mechanisms of anti-tumour action, validate novel targets and diagnostic tools specific to children affected with leukaemias or lymphomas.

The final aim is to develop a safe and efficient adoptive immunotherapy for children with advanced or refractory malignancies. CHILDHOPE particularly focuses on three paediatric tumours: acute B-lineage lymphoblastic leukaemia, non-Hodgkin B-lineage lymphoma and acute myeloid leukaemias.

Expected results

The originality of the CHILDHOPE project is to exploit the immunostimulatory properties of EBV-CTLs and retarget them to leukaemia/lymphoma cells, which themselves lack many of the costimulatory molecules needed to activate CTLs. Thus, our underlying general hypothesis is that expression of chimaeric antileukaemia/lymphoma receptors on EBV-specific CTLs will allow these cells to retain their known safety and functionality *in vivo* (ability to expand and regress in response to antigen load, to persist as memory cells, and to retain antiviral activity) in children with haematopoietic malignancies while adding safety, specificity and effector function directed to the residual leukaemia cells.

This strategy seems highly feasible since EBV-specific CTL lines have been generated and reinfused in numerous patients using robust and clinically validated methodologies developed by Brenner, one of our key scientific advisors in the CHILDHOPE project. Unmodified CD19 molecules have been manufactured and incorporated into EBV-CTLs, and tested *in vitro*. Our pioneering project now proposes to extend this approach against CD33+ malignancies, which represent a significant part of hard-to-treat paediatric leukaemias. Another major innovation is that we will investigate modifications to the chimaeric receptor molecule itself, in efforts to augment its capacity to enhance the transduction of signals that increase cytotoxic and memory effector function, while maintaining a high-level of safety. The T-cell proliferation should be strictly antigen-dependent and dwindle after elimination of the antigen.

Finally, the CHILDHOPE project moves the field forward as it brings to clinic this therapeutic modality in a phase I setting. We are confident that the chosen methods of gene transfer (i.e. retroviral vs. electroporation), in conjunction with our suicide gene system, will provide a safe albeit sufficiently prolonged antileukaemia effect *in vivo* in children with relapsed/refractory leukaemia/lymphoma. We anticipate that the antileukaemia/lymphoma effects – and consequently the survival of the treated patients – will increase with the chimaeric T-cell doses.

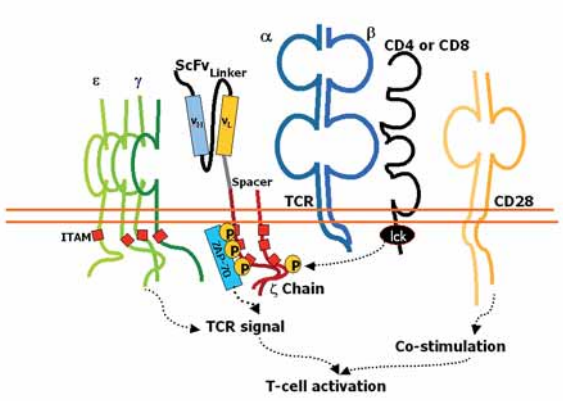
In parallel, the CHILDHOPE project will provide preclinical data comparing the cytotoxic potency of different T-cell subsets (EBV-CTLs, Cytokine Induced Killer T cells and chimaeric g9d2 T cells) in an effort to identify the best immune effector for future clinical application.

Potential applications

No animal model can fully dissect the tremendous complexity of the interactions between a human tumour and its host. The CHILDHOPE project is the first comprehensive attempt at administrating anti-tumour chimaeric T cells in children with haematopoietic malignancies. It represents a unique opportunity to address *in vivo* in a complete human environment some of the most fundamental hypothesis in the field of anti-tumour immunology. Our hypothesis is that targeting CD19 or CD33 will not only kill target cells but will also contribute to the release of yet unknown tumour-associated antigens (TAAs), which in turn may generate further immune activation. This mechanism known as antigen spreading may be of particular interest in tumours known for their propensity to induce antigen-loss variants. As these new TAAs may be either leukaemia/lymphoma-associated or have a broader scope of paediatric tumours, they may provide new targets for future immunotherapeutic approaches.

While the CHILDHOPE project focuses at this stage on three of the most frequent paediatric tumours (acute B-lineage lymphoblastic leukaemias, non-Hodgkin B-lineage lymphoma and acute myeloid leukaemias), our innovative technology should pave the way for the generation of T lymphocytes with an antibody-dictated specificity toward other tumour-associated antigen for which a monoclonal antibody exists. This in turn should allow us to redirect immune effectors towards other malignancies, including solid tumours, for which current therapeutic strategies are limited or have failed. This includes – but is not limited to – metastatic disease where T-cell therapies have had some success due to their capacity to migrate and infiltrate distant tumour sites.

In fact, it is likely that only a combination of therapies that act at key points of tumour escape pathways may help to eradicate tumour cells and also to lessen the dose-intensity of current chemotherapy regimen, a critical element of any therapeutic approach in developing individuals or in elderly patients who have reached maximum tolerable doses of anticancer drugs when their disease reoccur. Hence, our innovative therapeutic approach may provide hope for a cure for young as well as older patients with advanced or refractory tumours.



Chimaeric TCR shown in context of native TCR signalling complex. Single-chain variable region (scFv) is composed of heavy and light chain variable domains (VH and VL) which are connected by a short peptide linker. A flexible spacer connects VL allowing the antigen binding region to orient in different directions, improving antigen recognition. The spacer is then connected to the transmembrane and intracellular portion of CD3-z. The native TCR a and b chains are also shown alongside CD4/CD8. An unmodified CD3-z chain and CD3-e and CD3-g chains are also represented. Antigen binding to the native TCR leads to phosphorylation of CD3 immunoreceptor tyrosine-based activation motif (ITAMS, red boxes) which activate ZAP70, which in turn propagates further downstream signalling. Co-stimulation (in this case via CD28) is required for full T-cell activation.

Project number
LSHC-CT-2006-037381

EC contribution
€ 3 208 760

Duration
48 months

Starting date
01/11/2006

Instrument
STREP

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Keywords | Clinical trials | dendritic cell (DC) | genomics | HIV | immunotherapy | molecular cell biology | pre-clinical studies | proteomics |

DC-THERA

Dendritic cells for novel immunotherapies

Summary

Dendritic cell (DC) immunobiology has enormous potential for the development of new immunotherapies for cancer and infectious disease. Europe possesses a critical mass of leaders in the field who have pioneered many innovative advances and provided initial proof of principle for the approach. This Network of Excellent (NoE), DC-THERA, will integrate the activities of 26 participant groups of scientists and clinicians and six high quality SMEs across Europe. It will incorporate additional groups, particularly from future Member States, as associated members of the network. Their collective expertise and resources will be forged into an ambitious joint programme of activities to restructure the field. It will translate genomic, proteomic and bioinformatic information, with knowledge from molecular cell biology and pre-clinical models, into therapeutic endpoints: clinical trials of DC-based therapies for cancer and HIV. To this end, four thematic S&T clusters have been defined, with a fifth for horizontal activities. The latter includes development of synergistic links with other networks, providing benefit to EC programmes by underpinning all projects developing new vaccine strategies for major killer diseases. The network will implement an IT-based integrated knowledge management system and provide a centralised European resource of databases for the field. DC-THERA will develop new research tools, integrate existing and new technological platforms, recruit additional support staff, and make these available as shared resources for all partners. It will implement an ambitious Education and Training Programme, including new PhD studentships, a Visiting Scholars Scheme, high quality training courses, and a postgraduate degree in translational DC immunobiology. DC-THERA will contribute to the European biotechnology sector and have a major impact on European policy-making for the future. DC-THERA will evolve itself into a Centre of Excellence for DC Biology, with a lasting and global impact.

Problem

Dendritic cell (DC) immunobiology has enormous potential for the development of new immunotherapies for cancer and infectious disease. Europe possesses a critical mass of leaders in the field but they are geographically dispersed with localised resources.

Aim

This NoE, DC-THERA, will integrate the activities of 26 participant groups of scientists and clinicians and six high quality SMEs across Europe. It will incorporate additional groups as Associated Members of the Network. Their collective expertise and resources will be forged into an ambitious Joint Programme of Activities to restructure the field.

Expected results

The Network will translate genomic, proteomic and bioinformatic information, with knowledge from molecular cell biology and pre-clinical models, into therapeutic endpoints: clinical trials of DC-based therapies for cancer and HIV.

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LSHB-CT-2004-512074

EC contribution
€ 7 600 000

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60 months

Starting date
01/01/2005

Instrument
NoE

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www.dc-thera.org

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DC-VACC

Dendritic Cells as Natural Adjustments for Novel Vaccine Technologies

Summary

The immune system of vertebrate animals has evolved to respond to different types of perturbations, such as pathogens, whilst limiting self-tissue damage. Initiation of the immune response is accomplished by unique antigen presenting cells, called dendritic cells (DC) that are resting until they encounter foreign micro-organisms or inflammatory *stimuli.* Early-activated DCs trigger innate immune responses that represent the first line of defence against invading pathogens to limit the infections. Subsequently, activated DCs prime antigen-specific immune responses, which clear the infections and give rise to immunological memory.

Problem

Targeting of dendritic cells for vaccination and therapeutic intervention in infectious diseases and cancer.

Aim

The aim of DC-VACC project is to develop novel vaccine technologies and to use DCs as a natural adjuvant with specificity and minimum side effects and/or immunopathology. Early clinical trials have indicated that antigen-pulsed DCs do have great potential in the treatment of cancer. Such information will also be applicable in the eradication of infectious diseases. By defining novel reagents and protocols for the optimisation of DC as vaccines, this technology can then be translated to small biotechnology companies participating in this project. The basis of this proposal was to develop *in situ* DC targeting for use as vaccines in infectious diseases and cancer. Specifically, we are defining improved reagents and protocols for antigen delivery and targeting, which improve antigen processing and presentation by DC and can be used for vaccine technology. It will also be necessary to define optimal reagents and protocols for maturation and activation of mouse and human DC *in vitro* for use in vaccination so that optimisation of protocols for both species is comparable – thus preparing the way for use in pre-clinical models and clinical trials in future projects. There were, thus, two specific objectives for the project. The specific objective of work package 1 was to generate tools and methods for appropriate and efficient targeting and antigen delivery for the development of DC vaccine technology. This included the construction of viral and bacterial vectors, modification of RNA, peptides and proteins, and antibody development for specific targeting of DC receptor repertoire. A comparison is now under progress of peptides, proteins, RNA, DNA and antigen modifications that allow presentation via MHC molecules. Recombinant bacterial and viral vectors are amongst the most suitable vectors for the transduction of heterologous model antigens into DC.

The second objective, which is the basis of work package 2, was to define optimal reagents and protocols for maturation and activation of mouse and human DC *in vitro* for use in vaccination so that the optimisation of protocols for both species are compared to rapidly facilitate information from pre-clinical models being transferred rapidly to clinical trials in future projects. It is first necessary to identify optimal maturation *stimuli* of mouse and human DC by transcriptome analysis and functional assays. Thus the definition of such signals – including pathogen-derived products that trigger TLRs, ligands that trigger other DC receptors (such as FcR) and/or cytokines or cytokine inhibitors, and T-cell-derived molecules – is critical. The aim is to obtain a clear understanding of how DCs function to induce pro-inflammatory versus anti-inflammatory cytokines, chemokines and their receptors, and then how they function to activate CD4+ and CD8+ T-cells. In addition, it is essential that such activation signals are also be tested for their ability to process and present antigen to T-cells, leading to a protective Th1 response. A major unique innovative feature of this project is the close interaction and exchange between groups researching in mouse and human systems, which will rapidly facilitate the translation of basic findings to the clinic.

Expected results

The discovery and application of new adjuvants and targeting molecules, approaches for enhancing anti-tumour therapy and also in therapeutic intervention, and for vaccination in infectious diseases. Potential applications Enhancing anti-tumour therapy, approaches in therapeutic intervention and for vaccination in infectious diseases.

Potential applications

Enhancing anti-tumour therapy, approaches in therapeutic intervention and for vaccination in infectious diseases.

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STREP

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Dendritophages
Therapeutic cancer vaccines

Summary

The patient's blood monocytes are transformed into effector monocyte-derived dendritic cells (DC) (dendritophages), which fight the patient's own disease. The therapeutic cell drug comprises dendritic cells, which are loaded with cancer-specific antigens to activate the patient's immune system after re-injection.

This project aims to demonstrate the immune and clinical efficacy, reproducibility and feasibility of anticancer cell vaccine by choosing the best dendritic cell vaccination strategy via adequate pre-clinical studies (DC differentiation and maturation, tumour antigens selection and loading, dose delivered, site and vaccination schedule). It will monitor the immune response in correlation to the clinical response after defining the most relevant immuno-monitoring techniques, and will demonstrate the immunological efficacy of DC immunotherapy in prostate cancer, which will be performed after loading *ex vivo* dendritic cells with proteic antigen.

This will require the setting up of quality control criteria and data base design for the production of the cellular product, and optimising a GMP process. We will start a clinical trial to evaluate the cell drug on progressing prostate cancer patients.

Problem

- Select the most effective DC preparation.
- Develop GMP process.
- Show immunogenicity and safety in carcinoma patients.

Aim

The final goal of anticancer therapeutic vaccines is to prevent metastasis development as well as tumour progression and to provide long-term protection.

Previous and ongoing clinical studies have shown that there are no side effects associated with this type of dendritic autologous cellular drugs, and that immune and clinical responses can be achieved in some patients resistant to conventional therapies. The preclinical data generated on dendritic cells, as well as pilot clinical trial data, have driven the dendritic cell immunotherapy technology to reach adequate maturity to enter real standardisation and demonstration of immune efficacy. A phase I study of anti-tumour immunisation of patients with melanoma stage III or IV has been initiated during a previous EU Project coordinated by the same team, with autologous DCs (BIO-CT97- 2216, CELLULAR VACCINES, 1997). Nine patients had completed the treatment which consisted of four series of injections of dendritic cells pulsed with tumour cell lysate and dendritic cells pulsed with HbsAg and TetanusT.

Expected results

Results showed excellent safety and the presence of immune responses after vaccination, as well as signs of clinical responses in some of the patients. It is to be noted that one patient showed complete regression of metastases four months after the last vaccination, and another one showed stabilisation of the disease.

We have compared several technologies for obtaining DCs and selected the most appropriate for GMP development. The initial clinical results have been confirmed on a randomised clinical study conducted in malignant melanoma stage IV patients immunised with dendritic cells pulsed *ex vivo* with three melanoma cell lines lysates. The results of this study are based on 49 treated patients, with 15 patients having completed the cycle of six DC vaccinations, the others progressing due to late stage disease. No severe adverse event has been related to the therapeutic protocol nor to the DC product; the most frequent minor side effects were injection site reactions. Fourteen patients out of 49 initiated T-cell immune response against the antigens presented and ten patients had disease stabilisation; most of these immune responses and stabilisations were in the group of patients having received six vaccinations.

Studies are ongoing in colorectal and prostate cancer.

Potential applications

Vaccine therapy of metastatic carcinoma.

Project number
LSHB-CT-2003-503583

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Keywords | Protein-Protein interactions | small molecule inhibitors | knowledge driven drug design | blood/brain | tumour penetrant |

DEPPICT

Designing Therapeutic Protein-Protein Inhibitors for Brain Cancer Treatments

Summary

Protein-Protein interactions (PPI) are central elements in cellular processes and important targets for selective therapeutic agents. They constitute a rich area for discovery of novel small ligand-based therapies. This proposal seeks to utilise such interactions, in particular those featuring a a-helix binding groove such as p53-MDM2, or more novel targets, e.g. nm23-prune, to develop targeted small-molecule libraries with physico-chemical properties appropriate for therapeutic effect against various tumour types such as the brain cancers of glioblastoma and medulloblastoma.

Combination of the concepts below should provide an opportunity to unlock the potential of protein interactions as key components in signalling pathways via design of selective small-molecule modulators targeting the kinase-effector interaction instead of the ATP active site.

- Develop an understanding of the elements controlling selectivity in Protein-Protein signalling networks by developing approaches for design of small molecules that target a-helix binding groove interactions through use of structure-based and fragment-based approaches.
- Data-mining of ADME and drug-drug interactions to build a predictive database for library design.
- Develop quantitative structure/property relationships, with an emphasis on CYP-mediated metabolism, ABC transporters at the blood/brain and brain/tumour interfaces, mutagenicity, solubility, pKa, and passive permeability, and predictive tools for mutagenicity and other genetic toxicology end-points.
- Develop predictive PK and PBPK models to improve understanding of BBB and tumour penetration.
- *In vitro* and *in vivo* PK/PD and TK/TD characterisation of compounds, to increase understanding of their mechanism of action and reduce the use of laboratory animals.

Such knowledge-based approaches will also be applicable to design of small molecules for other Protein-Protein interactions utilising a a-helix binding groove both for peripheral tumours and other therapeutic areas.

Problem

Amongst the range of cancer types, brain and perhaps pancreatic cancers are especially lacking in effective treatments. In particular brain tumours are:

- the leading cause of death from childhood cancers among persons under 19;
- the second leading cause of cancer-related deaths in males aged 20-39;
- the fifth leading cause of cancer-related deaths in women aged 20-39.

Although onset of disease varies with tumour type, it can occur at a relatively young age causing additional and significant social and economic problems for both patients and their families.

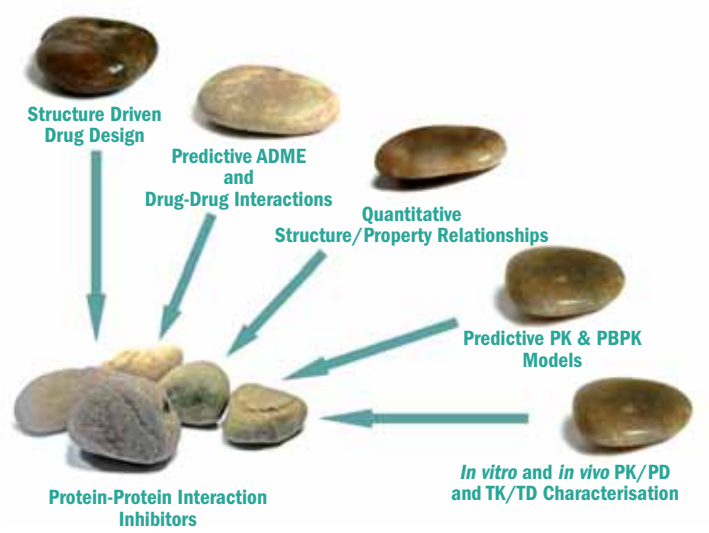
Current standard treatments include surgery, radiation therapy and chemotherapy. These may be used either individually or typically in combination. Brain cancers however present unique problems due to the location of the tumours: surgery and radiotherapy carry considerable risk to the patient and resection is not always possible. Chemotherapy is faced with the problem of penetration of drugs across the blood-brain barrier (BBB) and of lack of specificity. The focus for these patients is therefore on more effective therapies to prevent relapse, and on more efficient screening and diagnosis to halt the disease at an early stage.

Aim

The main objective of the proposed project is to provide more effective anti-tumour therapies by developing targeted small ligand libraries with appropriate physico-chemical properties for therapeutic effect targeted against Protein-Protein interactions implicated in various tumour types. The research activities will concentrate on knowledge-based approaches supporting translational research aimed at bringing basic knowledge through to applications in clinical practice and public health. The project will thus focus on providing small molecule ligands with minimal side effects as treatments for the brain tumours glioblastoma (GBM) and medulloblastoma.

Expected results

The successful integration of the various aspects of this proposal will provide a robust knowledge-based strategy for exploiting Protein-Protein interactions as drug targets in the treatment of brain tumours. The strategy should however be sufficiently generic to be transferable to other disease areas, especially within the CNS, where Protein-Protein interactions provide an entry point into disease-modifying therapies.



The individual components needed to achieve successful knowledge driven drug discovery will be combined to harness the opportunity for Protein-Protein inhibitors as potential small molecule therapies for brain tumours.

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Duration
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Instrument
STREP – SME

Project website
www.deppict.eu

Potential applications

The design of selective small molecule modulators of Protein-Protein interactions should provide the basis for developing new therapeutic strategies against brain cancers. They will allow for improving current libraries and for building predictive databases for library design of new specific drugs and therapeutic agents with high central nervous system penetration, necessary to reach a higher efficacy, selectivity, responsiveness and lower toxicity. In addition these approaches will represent a powerful system for preclinical data collection, leading to an optimisation of clinical trials setting and development.

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Keywords | molecular imaging | drug development | guided therapies | tumour diagnosis | *in vivo* imaging of gene expression |

EMIL
Molecular Imaging of Cancer

Summary

The general objective of EMIL is to bring together the leading European research teams in molecular imaging in universities, research centres and small and medium enterprises to focus on early diagnosis, prognosis and therapeutic evaluation of cancer.

The 58 partners of EMIL work around a common activity programme including:

- integration activities: creation of a network of technological and training facilities favouring the mobility of researchers and the integration of small and medium enterprises;
- dissemination activities: training, communication, common knowledge management and intellectual property rights;
- research activities: a common research programme making use of methodological tools of physics, biology and chemistry for the further development of molecular imaging (instrument techniques, molecular probes, biological engineering), and bringing together cancer imaging applications (early diagnostic imaging, development of new therapies, imaging for drug development).

Problem

Cancer is characterised by an uncontrolled proliferation of cells. For normal cells, controls operate at spatial level – a cell's location is defined by its integration in an organised tissue and temporal level – and a cell undergoes controlled division and death corresponding to its programmed life cycle. The last two decades have witnessed enormous advances in our understanding of cancer at the molecular level and demonstrated that it results from abnormal gene expression in cell clones. Gene expression analysis techniques are now witnessing systematic compilation of molecular data that can be used to provide accurate diagnosis and prognosis. These techniques are well established and widely applied to *in vitro* biological samples, but they destroy the sample during analysis and are not applicable to whole body and longitudinal explorations. Hence they fail to recognise the essential character of cancer development across time and space. On the other hand, *in vivo* imaging is a repeatable and non-invasive localisation technology with the potential to become the preferred means for cancer diagnostic and follow-up. However, imaging is based on evidencing a contrast between cancer and normal tissue, and this is quite challenging to perform *in vivo* in view of the fact that cancer cells are a clone of normal cells. Even though anatomic imaging can occur *in vivo* at sub-millimetre resolution, imaging techniques based on gross physical differences, such as density or water content, perform poorly in producing a contrast which must be based on specific imaging agents targeting tumour cells.

Molecular imaging is a new science bridging together molecular biology and *in vivo* imaging with the aim of detecting the expression of specific genes. Imaging science has made sufficient progress in the last decade to bridge the gap between physiology and molecular biology, and is now at the stage where it can perform molecular imaging of gene expression *in vivo.* Significant advances have occurred in molecular imaging modalities, including the nuclear medicine techniques of SPECT and PET, MRI and spectroscopy, which have attained resolution sufficient for small animal imaging, and optical imaging, which can now reach unprecedented sensitivities.

Aim

The potential of molecular imaging is considerable:

- in fundamental research, it allows the visualisation of cell function and molecular processes in living organisms – in particular the monitoring of the stages of growth and ageing, the response to environmental factors, the exploration of cell movements, etc.;
- in experimental medicine it identifies the molecular determinants of pathological processes *in situ,* evaluates new molecular therapies (such as gene therapy), and accelerates drug development (delivery of active compounds, efficacy of vectors, etc.).

With the evolution of imaging techniques and the capacity to transfer animal data directly into clinical applications, molecular imaging is a promising technique to tackle cancer detection, following the rule of the three Ps: Precocious, Precise and Predictive.

- Precocious: several successive mutations are necessary to make a cell cancerous. By detecting genetic anomalies at the very first mutation, molecular imaging could permit early diagnosis and prompt intervention at the start of the cancer-forming process.
- Precise: molecular imaging makes it possible to detect precisely, in space and time, the gene or genes that are dis-regulated in the cancer cell. A tumour can be characterised with molecular precision.
- Predictive: the fineness of the information obtained by molecular imaging allows it to determine the tumour type and to predict its evolution, adapt the treatment and monitor its efficacy.

This is essential to:

- validate, in the context of living organisms, the targets and drugs designed by genome data mining and *in vitro* gene expression analysis through non-invasive methods;

- acquire fundamental knowledge about the patterns of gene expression in normal tissues and define the changes in specific gene expression in cancer;
- design and develop drugs targeting cancer-related gene expression;
- allow precise evaluation of new treatments and new anti-cancer drugs that are required for progress in cancer management, through reliable measures of the cancer burden.

The general objectives of EMIL are:

- to coordinate the current effort in molecular imaging of Cancer in Europe by merging 43 groups from universities, research centres and SMEs coming from different scientific and technical fields into ONE virtual excellence centre with dedicated technological training platforms and integrated dissemination and management activities;
- to advance molecular imaging of cancer to the scientific, technical and economical status that should be expected from its value for European citizens, in order to improve cancer diagnosis follow-up, to promote and assist in the development of new targeted therapies, and translate science and technology progress into economical benefits;
- to act as leverage for a strong technological development that can be fuelled through specific research and development projects.

And more precisely:

- to optimise hardware and software for the integration of radiotracer, magnetic resonance and optical imaging data;
- to develop so called 'smart' imaging probes which are specific for a given molecular process and which can be detected and localised by at least one imaging modality;
- to use further developments of mouse models of human cancer to:
  - improve early detection of small cancer by advanced imaging;
  - directly study alteration of gene expression, tumour cell proliferation and migration *in vivo* over an extended period of time in the same animal;
- to identify *in vivo* molecular targets of cancer and metastasis enabling early diagnosis, assessment of disease progression and response to therapy;
- to establish imaging-guided patient-tailored therapies;
- to develop imaging technologies for *in vivo* drug screening using animal models;
- to apply molecular imaging of apoptosis to cancer.

Expected results

The present initiative is taken to capitalise on the extraordinary opportunity for studying non-invasively gene expression and function in cancer, due to recent advances in molecular imaging modalities. Because molecular imaging is fundamentally multi-disciplinary by nature, the instrument for this goal is a Network of Excellence bringing together genome-oriented scientists with various actors of imaging science and clinicians dedicated to formulating novel diagnostic methods based on imaging.

The EMIL Information System called EMIL Net (www.emilnet.org) will both facilitate the information flow between the partners and contribute to promoting molecular imaging of cancer.

Therefore EMIL Net will be dedicated to two different groups of users: the EMIL partners and the public:

- the public section will allow the free flow of information towards the end-users through the Internet site that will be used as a 'shop-window' of EMIL, the aim being to provide the molecular imaging community as well as the public with a tool that will spread excellence;
- the private section will be protected and accessible only to the 58 registered members. It will be used for management, knowledge and the Image database.

The EMIL Net private section:
The day-to-day management of the website will be secured by the management board to inform the EMIL partners on:

- research activities within the EMIL network;
- research outcomes: publications, common protocols, regulatory issues;
- career opportunities;
- training courses;
- education courses;
- knowledge management (consultation of documents, registrations to EMIL events, on-line reporting, consultation of work packages documents, discussion forum, etc.).

This will have an integrating action on the EMIL members who will visit the website to gather information on the network's events and activities. Members' access will be enforced progressively, with different levels of security.

Once the EMIL website is operating in good conditions, it will be upgraded with the final objective to create the EMIL database. This database will function as a reference server for molecular imaging of cancer. The web is a unique means to disseminate image information and more particularly animated data which cannot be shown on paper. EMIL will provide unique pharmacokinetics information visible on the website.

Potential applications

- Tumour diagnosis.
- Follow-up of tumour progression.
- Therapeutic evaluation.

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Keywords | Tumour progression | biomarkers | tumour escape | melanoma | prostate cancer | ovarian cancer |

ENACT

European Network for the identification and validation of antigens and biomarkers in cancer and their application in clinical cancer immunotherapy

Summary

Prospective clinical material will be collected during the life of the programme and new and existing tumour tissue, PBMC and serum banks will be available for use in the study. This common resource of material will be distributed to partners for the immunological, genomic, biochemical and proteomic analysis of tumour and host response(s) to immunotherapy. The results will be subjected to bioinformatic analysis in the context of clinical outcome of vaccine-based immunotherapy trials from five European clinical centres. Analysis of the results in the context of gender will allow prominent inter- and intra-tumour/host biomarkers to be identified for translation back into clinical practice.

Problem

Cancer remains a major health problem, with untold physical, psychological and economic costs to society. Elimination of cancer would reduce health care costs and enhance quality of life. Along with cardiovascular disease and ageing, it is currently the most intractable source of suffering and health care cost. Recent results from immunotherapy trials would suggest that inducing tumour-specific T-cell responses to tumour antigens can, in some patients, cause the regression of tumours or the stabilisation of the disease. However the mechanisms underlying the failure of immunotherapy to control and destroy residual cancer remains to be fully established. Experimentally, it can be shown that tumour rejection is mediated by CD8+CTLs aided by CD4+Thelper cell activity. However animals that fail to respond may fail to demonstrate a pronounced (if any) CTL response. In addition data from many laboratories have shown that tumour escape from CTLs can occur as a result of downregulation of MHC class I antigens, and in some instances cancer cells that show successive mutations may demonstrate progressive and complete loss of MHC expression. The current status of our understanding of adoptive cancer immunity also suggests that immune tolerance can equate with lack of response, with possible regulation by CD4+CD25+T-lymphocytes as well as other regulatory cells. Breaking tolerance through immunotherapy therefore represents one possible approach to promote T-cell responses and tumour regression.

Aim

ENACT aims to identify markers of response and tumour antigens that associate with ovarian, breast and prostate cancer and melanoma progression and resistance to immunotherapy. The present application will address these issues in a number of ways and directly analyse the important biomarkers that are expressed by cancer and may therefore be considered as novel targets by establishing a European network for collaboration. The cancer types to be included will address the issue of sex-related biomarkers associating with resistance to therapy. Cell biological, immunological, biochemical and molecular biology-based technologies will be used and knowledge generated in this project will not only result in a desired and highly competitive technological base for vaccine development (not necessarily restricted to cancer vaccines), but also will provide a better understanding of basic biological mechanisms underlying antigen presentation and recognition of tumours by CD8+ and CD4+ T lymphocytes and NK cells.

Expected results

- To establish a database for the analysis of clinical and experimental results in order to identify markers related to the outcome of immunotherapy.
- To provide clinical material and cancer cell lines for scientific investigation conducted within the programme.
- To assess the cellular and humoral immune response in patients undergoing immunotherapy.
- To identify biomarkers using proteomics and computer based algorithms.
- Assessment of the importance of immunological, genetic and proteomic biomarkers as indicators of therapeutic response related to gender.
- Dissemination of the information to the scientific community and the community at large.

Potential applications

The use of therapeutic cancer vaccines still has to be firmly established and previous clinical trials strongly indicate that not all patients benefit from receiving such treatment. The present study will allow us to establish whether the results of ENACT can be used in a clinical setting. The identification of indicators of patient response to immunotherapy would allow clinicians to target vaccination to those patients who are most likely to respond. The findings of the present study could result in assays that could be used to predict treatment outcome and/or monitor patients during the course of treatment. This would benefit the health care industry and patient care and the findings may be applicable to cancers other than those included in the research programme. The approach will allow us to gain further scientific understanding of the immune response to tumour antigens, which may influence the development of future generations of cancer vaccine. This research represents a valuable contribution to the welfare of patients who would be considered to be suitable candidates for vaccine-based therapy.

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European LeukaemiaNet

Strengthen and develop scientific and technological excellence in research and therapy of leukaemia (CML, AML, ALL, CLL, MDS, CMPD) by integration of the leading national leukaemia networks and their interdisciplinary partner groups in Europe

Summary

Leukaemias are a challenge to society and a cost factor because of their frequency in all age groups. They also serve as a model for a variety of diseases and possess exemplary relevance for basic research and patient care. Leukaemia research and therapy have achieved high standards and even a leading position in several European countries with regard to clinical trials, standardisation of diagnostics and molecular studies of signal transduction and gene expression. A true European world leadership, however, has not been accomplished yet due to national fragmentation of leukaemia trial groups, diagnostic approaches and treatment research activities and a need for central information and communication structures.

Problem

Leukaemia trial groups, diagnostic approaches and treatment research are currently fragmented. There is a clear need for benchmarking, information and communication structures at a clinical level in Europe.

Aim

The objective is to integrate the 95 leading leukaemia trial groups (chronic myeloid leukaemia (CML), acute myeloid leukaemia (AML), acute lymphoblastic leukaemia (ALL), chronic lymphoid leukaemia (CLL), myelodysplastic syndromes (MDS), chronic myeloproliferative disorders (CMPD), their 102 interdisciplinary partner groups (diagnostics, treatment research, registry, guidelines), industry and SMEs across Europe to form a cooperative network for advancements in leukaemia-related research and health care. Integration will be supported by central information, communication, education and management structures. Other goals are to intensify target and drug discovery, to shorten the time period to clinical translation, to apply advanced genomics, telematics and biotechnology to therapeutic progress and to promote research relevant also for solid cancers by large clinical trials. Furthermore, meta-analyses of specific subaspects, elaboration of prognostic scores, recognition of gender-specific differences, creation of uniform data sets for trials and registration, introduction of standards for diagnostics and treatment and development of evidence-based guidelines will be promoted throughout Europe. The proposed network will have the expertise and critical mass for European added value and world leadership. It will structure European research durably, spread European scientific excellence in the field of leukaemias and can start immediately. The 95 leukaemia trial groups and their 102 interdisciplinary partner groups representing several thousand participating centres and ten thousands of study patients treated within the trial groups form the backbone of the network. The network consists of 16 work packages. Of these, six deal with the various diseases (AML, ALL, CLL, CML, MDS, CMPD) and represent sub-networks on their own. Seven work packages represent interdisciplinary platforms which provide the support and research expertise required for high quality networking and excellence. Three core work packages provide central communication and management services for the whole network. The integration and interdisciplinary cooperation brings together 133 participants and approximately 1 000 researchers from 28 countries. The network will overcome national fragmentation and provide the critical mass to achieve research and treatment goals that cannot be achieved by single European countries.

Expected results

1. Establishment of central information and communication structures to create networks and platforms for all leukaemias and their interdisciplinary partners.

Integration is mediated by exchange of current trial protocols and procedures, information on participating centres and recruited patients and employment of uniform common data sets for comparable study outcomes and evaluations provided by the biometrical center (WP 17). This objective will be achieved through central services: Network Management Center (NMC, WP 1), European Leukaemia Information Center (ELIC, WP 2) and Central Information and Communication Services (CICS, WP 3). The central service groups benefit from a three years' experience in similar tasks for the German Competence Network for Acute and Chronic Leukaemias funded by the German Ministry for Education and Research (BMBF) and provide the basis for a head start of the network. These groups will also provide training programmes, workshops, symposia, exchange of researchers and information programmes, thereby spreading excellence to health care personnel, researchers and to other countries not yet participating in the network. With the support of NMC (WP 1) the network will be managed in a two-layer networking organisation. Clinical trial groups for each leukaemia and their interdisciplinary partner will form their own European subnet organizations with coordinators, steering

groups and management structures. These subnets and platforms will then be integrated in the European Leukaemia Network which will conduct the integrated research programme detailed below. The network will be managed by the Network Coordinator (NC), the Scientific Network Manager (SNM) and the Steering Committee (SC) consisting of the coordinators (=Lead participants) of the work packages (WP). The University of Heidelberg will provide the expertise for financial, legal and contractual management.

2. Set-up of European networks for each leukaemia and related syndrome.

These networks will comprise the national trial groups for each leukaemia and represent the first stage of networking and European integration.

3. Set-up of European platforms for each interdisciplinary specialty.

These platforms are sub-networks of excellence of diagnostic, therapeutic and biometric research groups on their own and constitute interdisciplinary partners enabling the clinical trial groups to achieve the high quality patient care and research required for European leadership.

4. Performance of clinical trials (all leukaemias).

Employing uniform common data sets the trial groups will continue their current trials funded by alternative sources and will start new trials using diagnostic standards established by the diagnostic platforms (WPs 10-13). Criteria for accreditation of trials will be set up.

Lung infection and inflammation is a growing problem within all states of the EU, and the infections are routinely treated with antibiotics. The pharmaceutical industry is interested in the development of protein therapeutics, which can be used as alternatives to antibiotics. There is a relatively fragile protective barrier, the alveolar lining layer, which controls the interaction between the atmosphere and the lung. The film, known as lung surfactant, plays two important roles, prevention of lung collapse during respiration and provision of a first line of defence against the extremely varied range of particles, allergens and microbes that are present in the environment. The lung surfactant is a surfaceactive mixture of phospholipids and four main surfactant proteins – SP-A, SP-B, SP-C and SP-D. The SP-B and SP-C proteins are small, highly hydrophobic, polypeptides, which are strongly associated with the phospholipid portion of the surfactant, whereas SP-A and SP-D are large (approximately 600kDa) and complex, disulphide-bonded, proteins of a more hydrophilic nature. They can bind, via their lectin domains, to arrays of carbohydrate structures on the surfaces of pathogenic microbes and to glycosylated allergens, thus initiating defence against a range of viral, fungal and bacterial lung infections and modulating allergic reactions. There is evidence of lowered levels of SP-A, and SP-D, in the lung surfactant of a growing number of types of infection- or allergy-mediated lung inflammation, which strengthens the case for testing the use of recombinant forms of these proteins as therapeutic alternatives to antibiotics.

5. European Registry (all leukaemias).

A European registry will allow to determine incidence and disease patterns across Europe including gender, age and ethnic differences, investigate familiar aggregations, overlap syndromes or precursor conditions, explore risk factors associations and differences in gene environment interaction, using data from cytogenetic analyses (WP 11) and genomic profiling (WP 13), perform quality of life assessments, recognize sub-entities on the basis of cytogenetic or gene profiling information, follow-up patients for the development of prognostic scores for old and new therapies and determine proportions of patients in individual countries treated on specific protocols or with specific therapies e.g. SCT (WP 14). The registry will be run by the expert group Biometry for Registry, Epidemiology, Metaanalyses and Prognosis (WP 17). This group has gained a long-standing broad experience in collecting data, performing meta-analyses and establishing prognostic scores. The database established by the network will have far-reaching implications for research and public health planning far beyond the period of EC funding.

6. Standardisation.

Standardised and quality controlled diagnostic procedures and therapies constitute the basis for improvements of clinical outcomes. This concerns all diagnostic approaches such as morphological diagnosis of blood and marrow cells (WP 10), cytogenetics (WP 11), detection of minimal residual disease (WP 12) and gene expression profiling (WP 13) as well as therapies such as transplantation, anti-infection prophylaxis and treatment and the testing of new drugs in phase I/II trials (WP 14 and 15). The establishment of standards for a wide spectrum of diagnostic and therapeutic applications will raise the quality of research and patient care beyond the period of EC funding and will predictively have a profound impact on outcome as measured by prolongation of life and cure rates across Europe.

7. Meta-analysis and guidelines.

Whenever randomised trials are available for analysis (mostly CML and AML), meta-analysis will be performed and published (WP 17). On the basis of meta-analysis, evidence-based guidelines will be worked out and used for the improvement of patient management and for educational purposes (training programmes, workshops in associated countries, exchange of researchers and physicians for training purposes). Meta-analysis will be also performed on combined data sets with rare subtypes of leukaemias (WP6).

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European MCL Network

European Mantle Cell Lymphoma Network: Translation evaluation of molecular prognostic factors and pharmacogenomics in European interdisciplinary collaboration

Summary

Mantle cell lymphoma (MCL) is a subtype of malignant lymphoma with an especially poor prognosis. Recently, a European MCL Network of clinicians, basic scientists and pathologists has been established to investigate the clinical as well as molecular aspects of MCL. In previous clinical trials, the superiority of innovative treatment options (high dose therapy, combined immuno-chemotherapy) has been confirmed, and cell proliferation has been identified as the most important prognostic factor. Based on these extensive prerequisites, we have initiated a translational approach to evaluate innovative treatment options (like immuno-chemotherapy, radioimmunotherapy, high dose consolidation and molecularly targeted approaches) and molecular prognostic markers in prospective randomised studies. All study cases are subjects of innovative molecular analyses and continuous detection of minimal residual disease. This translational approach will not only lead to more effective therapeutic strategies based on the molecular profiling but also pave the way to molecular targeted treatments.

Problem

Mantle cell lymphoma (MCL) is a distinct, clinically very aggressive subentity of malignant lymphoma with a median survival of three years. However, a small subset of patients represents long-term survivors. So far, the discriminative power of different prognostic parameters has been limited and did not allow the reliable identification of the individual patient's risk profile. Thus, a better understanding of the underlying molecular mechanisms is eagerly warranted.

Aim

Based on the previously established European MCL Network of clinicians, basic scientists and pathologists and the recent development of innovative molecular techniques (matrix CGH, RNA array chips, RQPCR, proteomics), we are performing a global approach to investigate innovative treatment options of MCL and evaluate new predictive (pharmacogenomics, minimal residual disease) and prognostic molecular markers (genomic alterations, RNA/proteome profiles) in controlled prospective studies. This translational approach of the European MCL Network will not only lead to more individualised therapeutic strategies based on the molecular risk profile but will also finally elucidate the way to future molecular targeted treatment options in a subtype of malignant lymphoma with an otherwise dismal clinical outcome.

Expected results

- Prospective evaluation of combined immunochemotherapy and myeloablative consolidation in patients <65 years: R-CHOP followed by myeloablative consolidation vs. R-CHOP/R-DHAP followed by high dose Ara-C therapy.
- Prospective evaluation of combined immunochemotherapy and different maintenance strategies in patients >65 years: R-CHOP vs. R-FC followed by IFN vs. Rituximab maintenance.
- Regular histomorphological panel review of study cases (subtyping according to cytological criteria).
- Prospective evaluation of a panel of proliferation-associated and new oncogenic markers (immuno-histochemistry).
- Prospective evaluation of MRD detection (PCR, FACS, FISH) in the patient cohort of the European MCL Network.
- Prospective evaluation of the proliferation-associated gene signature in the patient cohort of the European MCL Network (RNA array).

Potential applications

Malignant lymphoma is currently the fourth most frequent malignant disease and displays the highest increase in annual incidence of all hematological neoplasias. In this regard, the exploration of innovative treatment strategies and evaluation of prognostic markers in the rather rare disease of mantle cell lymphoma is also a model disease for much more frequent diseases which have a profound impact on the public health system as well as the general society. The prospective studies of the European MCL Network studies will enable us to gain a deeper understanding of the pathophysiological network of cell programme regulation in malignant lymphoma. In addition, applying this multivariate procedure, the critical biological players of malignant transformation will be identified which may represent the suitable target genes of future treatment strategies in a disease with otherwise dismal prognosis. Moreover, this collaboration of outstanding clinical as well as molecular scientists will be a paradigm for other fields of biological research interlinking clinical and basic science as well as scientific excellence from all over Europe.

Project number
LSHC-CT-2004-503351

EC contribution
€ 2 493 900

Duration
42 months

Starting date
01/07/2004

Instrument
STREP

Project website
www.lymphome.de

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Keywords | Hypoxia | HIF | pericellular | human | drug |

EUROXY

Targeting newly discovered oxygen-sensing cascades for novel cancer treatments

Summary

A five-year effort to develop anti-cancer drugs targeting the hypoxia responsive regulatory pathways in human cells was finished the first two years. It has led to a better understanding of the therapy resistance of cells at hypoxia and a much more detailed knowledge about the pathways involved. To work under controlled conditions, *in vitro* and *in vivo* technology has been developed to keep and record the peri cellular oxygen tension. It is still unclear if the preferred target for intervention will be the cells oxygen sensors upstream from HIF or HIF itself or one of the downstream molecules like the hypoxia induced electron pumps for which we are patenting new inhibitors.

Problem

Most solid human tumours have areas where the cells are exposed to low oxygen tension. Low oxygen tension is correlated with a bad prognosis. Hypoxic tumour tissues usually have a lowered susceptibility to conventional treatment with irradiation and cytostatics.

Aim

The consortium want to develop a new class of anti-cancer agents targeting and disrupting the adaptive mechanisms exploited by human cells when exposed to low oxygen tensions.

Expected results

Within the remaining three years, the consortium expects to have a better knowledge of the cellular responses to low oxygen tension and to know regulatory molecular pathways important for cell adaptation to hypoxia.

The consortium also expects to have developed a technology platform for measuring pericellular oxygen tensions *in vitro* and *in vivo* and to have methods for non-invasive determination of oxygen tensions.

We further expect to have *in vitro* and animal tested a few novel and patented compounds for cytostatic effects on human cancer cells kept at *in vivo* relevant low oxygen tension.

We ultimately hope to have compounds that will attract private companies to undertake further development work.

Potential applications

Anticancer drugs.

Project number
LSHC-CT-2003-502932

EC contribution
€ 8 000 000

Duration
60 months

Starting date
01/02/2004

Instrument
IP

Project website
www.euroxy.info/

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Keywords | Radiation-induced complications | adult stem cell therapy | cancer therapy |

FIRST

Further improvement of radiotherapy of cancer through side-effect reduction by application of adult stem cell therapy

Summary

Radiotherapy is the second most important treatment modality after surgery in the treatment of cancer. At present over 50% of all cancer patients receive radiotherapy at one stage in their course. Inevitably normal tissues are also exposed to ionising radiation during radiotherapy of tumours. This can result in organ failure and hence can seriously limit the treatment dose. Reduction of the side-effects of radiotherapy will not only increase the quality of life after the treatment but may also result in increased survival of cancer patients as it will allow dose escalation to the tumour. This is true even if the most optimal physical dose delivery (conformal therapy, protons) of radiation is applied. Radiationinduced organ failure is mainly caused by stem cell sterilisation, leading to a reduced reconstitution of functional cells. The innovative vision of this project is to reduce radiation-induced complications through stem cell therapy. Replenishment of the depleted stem cell compartment should allow regeneration of irradiated tissues. A successful replacement of stem cells and subsequent amelioration of radiation-induced complications may open the road to completely new strategies in radiotherapy and help combat cancer.

Problem

Many attempts have been made to attenuate radiation-induced damage to normal tissues. Although much knowledge has been obtained on the mechanism of radiosensitivity of normal tissue, and the pathogenic pathways that eventually result in loss of function, the vast majority of remedies are either inadequate, diminish in time or have not been shown to be selective for normal tissue only. Therefore a completely new approach is needed. Today bone marrow transplantation is common clinical practice. Due to new scientific knowledge and biotechnological developments, only recently it has become apparent that bone marrow transplantation may rescue other organs. Moreover, cells from certain tissues may even repopulate the haematopoietic system. Similar findings have been reported for stem cells derived from other tissues than bone marrow. However, tissue specific cells are only available in small numbers. Therefore, bone marrow stem cells have the largest clinical potential to be used for transplantation into irradiated organisms or individual normal tissues to provide the organ with sufficient numbers of cells necessary for regeneration.

Aim

The aim of the project is to develop and optimise techniques to prevent radiation-induced normal tissue complications using adult stem cell therapy. The tissues of interest will be oral mucosa, skin, gut and salivary gland tissues. The first step will be to provide proof of principle for the impact of stem cells on the repair of irradiated tissues.

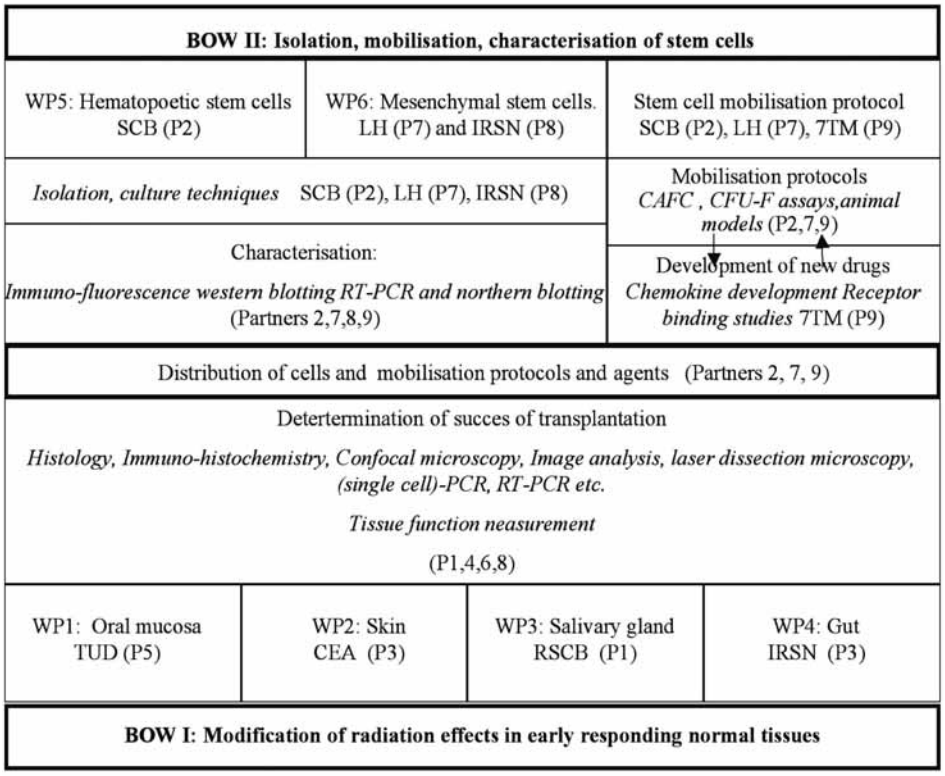
To this end protocols for the isolation, mobilisation, and characterisation of bone marrow derived stem cells will be performed and developed. Specific targeted approaches for transplantation of bone marrow derived stem cells will be designed and tested.

Expected results

- Optimised protocols for isolation, generation, mobilisation, characterisation and expansion of stem cells from bone marrow.
- Demonstration of proof of principle for the use of bone marrowderived stem cells to modificate radiation-induced normal tissue damage in animal models.

Potential applications

The resulting scientific and (bio)technological knowledge and a successful replacement of stem cells and subsequent amelioration of radiation-induced complications may eventually lead to new and improved cancer treatment strategies which will profoundly increase radiotherapy treatment success.



The blocks of work (BOW) are divided into work packages (WPs). WPs 1-4 are the normal tissues studied. They use the methods described to determine the success of transplantation. WPs 5-8 concern the different stem cell types and protocols. Common techniques are shared and are distributed to BOW 1. TUD (P5): Medical Faculty Carl Gustav Carus, Radiobiology Laboratory, Prof. Wolfgang Dörr (DE). CEA (P3): Service de Génomique Fonctionnelle, Dr. Michèle Martin (FR). University of Groningen, RSCB (P1): Radiation and Stress Cell Biology, Dr. Robert Coppes (Coordinator, NL). IRSN (P3): Département de Radioprotection de la Santé de l'Homme et de Dosimetrie, Dr. Dominique Thierry (FR). SCB (P2): University of Groningen, Stem Cell Biology, Prof. Gerald de Haan (NL). LH (P7): Université François Rabelais, Faculté de Médecine, Laboratoire d'Hématopoïèse, Dr. Pierre Charbord (FR). 7TM (P9): 7TM Pharma A/S, Hørsholm.

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LSHC-CT-2004-503436

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Duration
30 months

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01/09/2004

Instrument
IP

Project website
www.rug.nl/med/onderzoek/internationaleprojecten/europeseprojecten/first

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Keywords | Gene therapy | adenovirus | non-viral vectors | prostate cancer | gene promoters | stealthing | re-targeting |

GIANT

Gene therapy: an integrated approach for neoplastic treatment

Summary

The translation of genetic knowledge from the human genome into disease-specific therapy for untreatable congenital disorders and acquired diseases is now becoming a reality. However, the gene therapy vectors currently used in experimental settings can be developed for safe clinical application only if fundamental problems are solved; i.e. the limitation of vector dose by attachment targeting and expression control, and a decrease of non-specific toxicity. Minimisation of vector immunogenicity (stealthing) is necessary to reduce bloodstream and immune-mediated reduction of effective vector concentration.

GIANT will therefore concentrate firstly on one uniform model system and disease target (prostate carcinoma) for vector testing standardisation and *in vitro,* preclinical and clinical vector comparison. We will use a clinically approved vector backbone of adenoviral constructs re-targeted to prostate cancer via surface antigens, and hybrid prostate-targeted promoters. The consortium includes a GMP vector production facility and clinical facilities with scientific and ethical permission to carry out human cytotoxic gene therapy trials, guaranteeing efficient translation of selected vectors into clinical testing. The biomaterials obtained will serve to develop new assays for vector distribution, efficacy and monitoring of the immune response against various vector systems.

The GIANT participants have a long record of EU-based scientific collaboration and expertise in ethically approved clinical vector generation. The SMEs own international patents on retargeting vectors and target discovery methods, providing a technology platform for further exploration of promising targets and innovative approaches to facilitate treatment of neoplastic diseases.

Problem

Prostate cancer, particularly in its advanced stages, remains refractory to conventional therapies and is therefore a good target for gene-based therapies. However, without adequate specificity and a fundamental knowledge of the parameters which reduce efficacy when vectors developed in tissue culture are employed in human subjects, these new gene-based therapies will fail to become established in clinical practice.

Aim

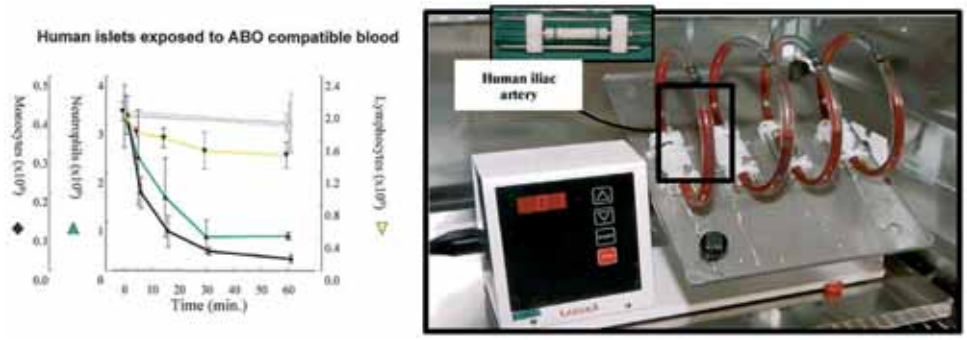
The aim of the GIANT project is to produce a range of prostate targeted and stealthed viral and non-viral vectors for ultimate testing in Phase I clinical studies.

Expected results

- New generations of gene transfer vectors, targeted to prostate cancer cells.
- Stealthed vectors that have a longer half-life and efficacy in human tissues.
- International multi-centre, Phase I clinical trials of gene therapy for prostate cancer. Acceptance of gene therapy for prostate cancer in the European Urological Community.

Potential applications

- Gene therapy for prostate cancer.
- Safe, targeted vectors for human gene transfer.
- A greater understanding of the human immune response against gene transfer vectors.



Immunogenicity testing model.

Project number
LSHB-CT-2004-512087

EC contribution
€ 9 683 102

Duration
60 months

Starting date
01/01/2005

Instrument
IP

Project website
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Keywords | Dependence receptors | apoptosis | tumour suppressor |

HERMIONE

Novel Anticancer Therapeutics based on Modulation of Apoptosis through Dependence Receptors

Summary

Receptors are usually seen as inactive unless bound by their ligand. However, a new concept has emerged since 1998, by which some receptors can in fact mediate two different signalling pathways, depending on the presence or absence of their ligand. Studies of such receptors have indeed revealed that, in the absence of ligand, signalling initiates an active process leading to cell death via apoptosis, whereas programmed cell death is inhibited in the presence of the ligand. Therefore, expression of these receptors leads to a state of cellular dependence on their respective ligands, which is why they have been named 'Dependence Receptors' (DRs). The different DRs trigger apoptosis in the absence of ligand, suggesting that they may all act as regulators of tumourigenesis. In addition, expression of DRs is lost or decreased in many tumours, suggesting that they act as tumour suppressors and that their loss represents a selective advantage for tumour cells.

HERMIONE proposes that unravelling the link between different DRs (DCC, UNC5H, KAI1 and RET), downstream molecules and apoptosis will lead to the identification of new potential targets for anti-cancer drugs. The project will provide a better understanding of the signalling pathways acting downstream of DRs, observe the association of mutations with the onset and progression of tumours (grade, prognosis), and generate murine models in which the apoptotic signalling of the DR is turned off to study the implication of DRs in tumourigenesis *in vivo.* Through this, HERMIONE will generate knowledge on DR-signalling pathways involved in the apoptosis of tumoural cells (colorectal, breast, thyroid and prostate cancers) and use the general concept of Dependence Receptors to select and perform pre-clinical testing of novel anti-cancer drugs.

Problem

Colorectal, breast and prostate cancer are among the commonest forms of cancer in Europe. Breast cancer is the main cause of death by cancer, killing over 400 000 women a year. There is no efficient treatment against metastatic breast tumours and available anti-cancer treatments are imperfect, therefore the probability of cure is not high. Existing treatments are highly toxic to normal tissue and cause substantial loss of life quality. Surgery, chemotherapy and radiotherapy are very invasive, and advanced stage cancer patients treated with cytotoxic therapeutics are often subject to debilitating side- effects. Therefore, there is a great need to develop more precise therapeutics, to reduce side-effects and improve the overall wellbeing of treated patients.

Aim

The aim of HERMIONE is to understand better how dysfunctions in DR-signalling can lead to tumour formation and/or progression. The generated knowledge will be applied to the development of targeted drugs, to provide safer and more effective treatments for patients.

The following models, by which DRs regulate tumour initiation, progression and metastasis, can be surmised from current knowledge on DR-signalling and illustrate the project's hypothesis that these receptors act as tumour suppressors via their pro-apoptotic activity: in a normal context: the receptor is bound by its ligand and induces a positive signal (survival, differentiation, etc.). In the case of genetic alteration leading to cell transformation and thus cell proliferation, the concentration of ligand in the extracellular environment becomes insufficient to bind all receptors. In some cases, cells acquire the property to migrate into the blood circulation and/or invade other tissues where the ligand is absent. Unbound dependence receptors consequently trigger apoptosis.

According to these models, a selective advantage for a tumour cell would be to lose the death activity of DRs by mutation, to curb their expression or to acquire autocrine expression of the ligand. Therefore, Dependence Receptors appear to be original targets for combating cancer and potential candidates to be studied in the aim of developing novel cancer therapeutics. In order to achieve this, proper understanding of the way these receptors induce apoptosis, i.e. deciphering the signalling pathways operating downstream, is of great importance.

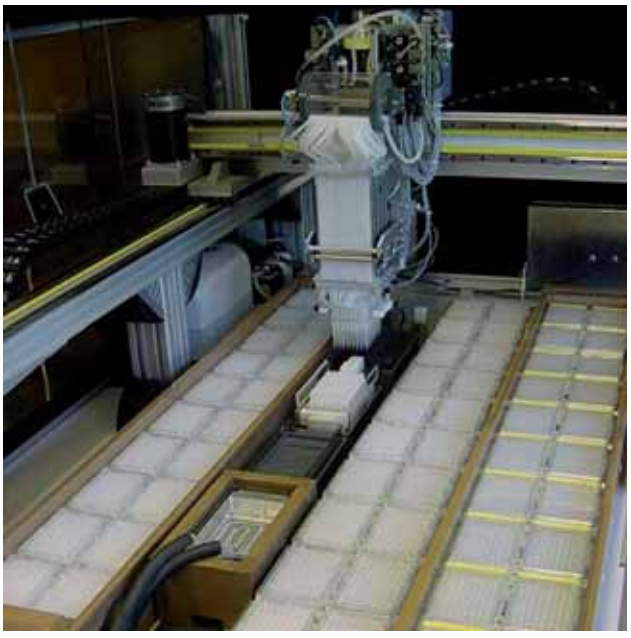
Expected results

- Understanding the fundamental phenomena:
  - to yield better understanding of the signalling pathways that act downstream of dependence receptors. Understanding the way Dependence Receptors are linked to the trigger of apoptosis will provide targets for drug development;
  - to analyse the status of DR/ligand pairs in human tumourigenesis: is there a selective advantage to losing expression of the receptor, gaining autocrine expression of the ligand or losing death function by mutation? From these studies, clear links between DRs and tumour progression will be established, thereby generating new markers for prognosis.

- Applying scientific knowledge to the identification and pre-clinical validation of novel anti-cancer drugs:
  - generation of new markers for tumours, valuable tools for prognosis;
  - development of peptides and monoclonal antibodies: by studying different DRs and their respective ligands, the Consortium will validate targets in mouse models through the development of recombinant proteins and monoclonal antibodies;
  - development of anti-cancer agents: the data collected through this project will provide the basis for the development of small molecules as anti-cancer agents.

Potential applications

HERMIONE will enable better understanding of how dysfunctions in dependence receptors signalling can lead to tumour formation and/or progression. The knowledge generated will be applied to the generation of targeted drugs, providing safer and more effective treatments for patients. The work performed within this project will include the development of new biomarkers that will provide means for both diagnosis and prognosis. The amount of fundamental knowledge generated within the project will allow better comprehension of the events linking dependence receptors to tumour progression and provide targets to modulate apoptosis of tumour cells. This will provide valuable data to identify Dependence Receptors that could be involved in other types of cancer.



Screen for apoptosis genes by highly specialised custom-made robots.

Project number
LSHC-CT-2006-037530

EC contribution
€ 2 364 909

Duration
36 months

Starting date
01/11/2006

Instrument
STREP

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http://hermionetypo.prodige.com/

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Keywords | Photodynamic therapy | antibody-photosensitiser conjugates | tumour neovasculature |

Immuno-PDT

Immunophotodynamic therapy of cancer: concepts and applications

Summary

Photodynamic therapy of cancer, i.e. the generation of reactive oxygen species in the tumour environment which follows the irradiation of suitable photosensitising molecules, is an attractive modality for the selective ablation of inoperable superficial neoplastic lesions. In this project, we have put together a network of academic research groups and companies for the development of antibody-based targeted photodynamic therapy modalities.

The planned research activity starts with the synthesis of novel photosensitising molecules suitable for conjugation to antibodies, and with the identification of novel human monoclonal antibodies capable of a selective targeting of the tumour neovasculature for immuno-PDT applications. Following an extensive *in vitro* characterisation of the most promising antibody-photosensitiser conjugates, the therapeutic potential of the best conjugates will be tested in rodent models of cancer, paving the way for future clinical applications.

Problem

Cancer chemotherapy is generally accompanied by severe side effects, mainly due to unspecific cytotoxicity of classic antineoplastic treatments. Photodynamic Therapy contributes to a significant efficacy in the treatment of neoplastic and abnormal tissues, using a combination of photosensitiser, such as porphyrin, chlorin, bacteriochlorin or phthalocyanine derivatives, and tissue-penetrating visible laser light. Laser light promotes the photosensitiser to its excited state. The photosensitiser, in turn, interacts with molecular oxygen and returns to its ground state, resulting in the generation of the highly localised cytotoxic agent, singlet oxygen, which ultimately affords tumour destruction.

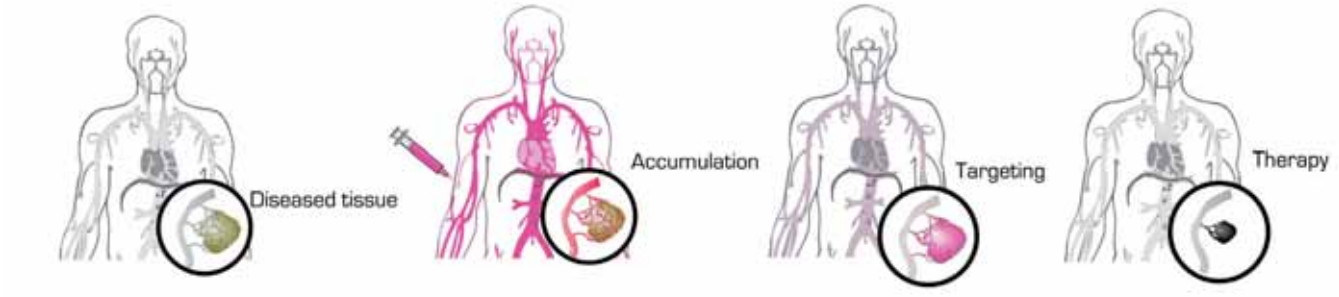
PDT is a modality of cancer treatment that causes cytotoxic action only locally in the region of exposure to laser light with a specific wavelength matching the absorption profile of the photosensitiser, thus leading to very site specific toxicity. The targeted delivery of photosensitisers to suitable neoplastic sites is likely to increase the scope and the efficacy of PDT therapy still further. The antibody-mediated targeted delivery of photosensitisers to the tumour neovasculature mediates a rapid occlusion of blood vessels, thus depriving tumour cells of oxygen and nutrients and triggering an avalanche of tumour cell deaths. As an additional benefit, lower doses of photosensitiser can be administered, thus reducing problems of skin photosensitivity.

Aim

The present project has as objectives the synthesis and conjugation of novel infrared photosensitisers to the most promising antibodies against vascular tumour antigens obtained by human antibody technology, the immunohistochemical characterisation, the biodistribution and imaging targeting *in vivo,* in order to select the best antibody-photosensitiser conjugates to be taken forward into clinical trials as a final objective.

In details, the objectives are:

- the synthesis of novel infrared photosensitisers with sufficient water solubility (i.e., not sticky to unwanted cells and tissues), which absorb in the near-infrared light spectrum and which efficiently generate singlet oxygen and/or other reactive oxygen species;
- screening of phage display libraries to find the most suitable antibodies for the project;
- investigation of a novel method for the conjugation of the antibody and photosensitiser molecules. We propose to investigate the coupling of photosensitisers to antibodies, based on the non-covalent but stable interaction of photosensitising molecules with specific antibody fragments or suitable single domain binders;
- evaluation of the conjugates *in vitro* e *in vivo*. Our novel PDT agents will be extensively tested *in vitro,* in order to ascertain whether non-covalently bound photosensitisers can retain singlet oxygen production activity upon irradiation.



The agents will be tested in rodent models of cancer and, if successful, will open novel therapeutic opportunities for the selective treatment of superficial tumors in accessible body cavities.

Expected results

Most importantly, there is a reasonable expectation of a medical benefit for cancer patients stemming both directly and indirectly from this project:

- directly, since immuno-PDT procedures promise to be invaluable for the selective ablation of inoperable superficial neoplastic lesions, such as certain head&neck, gastrointestinal, urogenital and gynecological tumours;
- indirectly, since the knowledge generated by the validation of novel antibodies for vascular targeting applications is likely to have an impact in other forms of immunotherapy, including the use of full IgGs and antibody-cytokine fusions for cancer therapy.

Potential applications

When considering immuno-PDT applications in oncology in a strict sense, the potential market is directly determined by the incidence of inoperable superficial neoplastic lesions, such as certain head&neck, gastrointestinal, urogenital and gynecological tumors, which would benefit from a PDT-based ablation.

In a broader sense, discoveries in terms of new tumour targets, new antibodies, new coupling methodologies and new photosensitisers will benefit several areas of biomedical development, including non-oncological indications such as potentially-blinding angiogenesis-related ocular disorders (age-related macular degeneration, diabetic retinopathy).

Project number
LSHC-CT-2006-37489

EC contribution
€ 3 000 000

Duration
36 months

Starting date
01/10/2006

Instrument
STREP – SME

Project website
www.immunopdt.net

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Keywords | Ovarian cancer | thymidylate synthase inhibitor | small molecule inhibitor design |

LIGHTS

Small ligands to interfere with Thymidylate Synthase dimer formation as new tools for development of anti-cancer agents against ovarian carcinoma

Summary

Ovarian cancer is the fifth most common cause of death from cancer in women. The standard first-line treatment is a combination of paclitaxel and carboplatin or carboplatin alone. In the case of progressive disease or drug resistance treatment with platinum, either alone or in combination, especially investigational compounds should be used. The mechanisms behind acquired resistance to cisplatin (cDDP) and its derivatives are not clear yet, although it is evident that the process is multifactorial, including enhanced DNA repair. In the human ovarian carcinoma cell line A2780, a three-fold-cDDP- resistance was associated with cross-resistance to the thymidylate synthase (TS) inhibitor 5-fluorouracil and to methotrexate, a 2.5-fold increase in TS, and an increase in the intracellular pools of the TS cofactor 5, 10-methylentetrahydrofolate and of tetrahydrofolate.

The ultimate goal of LIGHTS is to directly halt tumour progression and the development of drug resistance upon treatment with platinum-derived drugs, by inhibiting the protein regulatory function of monomeric TS through small molecule cellular perturbation. The scientific and technological objectives will be to design small-ligand libraries to bind to the TS monomer (dimer interface) and thereby disrupt TS. The strategy will include, systems pathway analysis, protein SH-labelling to identify low-affinity ligands, peptide mimic design and synthesis, and filtering for ADME properties.

The multidisciplinary approach will be carried out by a Consortium integrating molecular modelling, chemistry, chemoinformatics, structural biology and pharmacology, and will apply the knowledge being created by genomics and other fields of basic research to the problem of discovery of anti-cancer agents. The Consortium consists of six groups from five different countries, including three SMEs.

Problem

Ovarian cancer is the fifth most common cause of death from cancer and the most common cause of death from gynecologic cancer in women of all ages in the Western world. Single-agent carboplatin (cDDP) has been considered a reasonable option for first-line chemotherapy for ovarian cancer. However the occurrence of resistant cell populations in the tumour, limiting the usefulness of the platinum drug, represents a growing problem. Resistant cells often become refractory to the initially used drugs and are extremely difficult to eradicate, therefore the use of drug combinations is necessary.

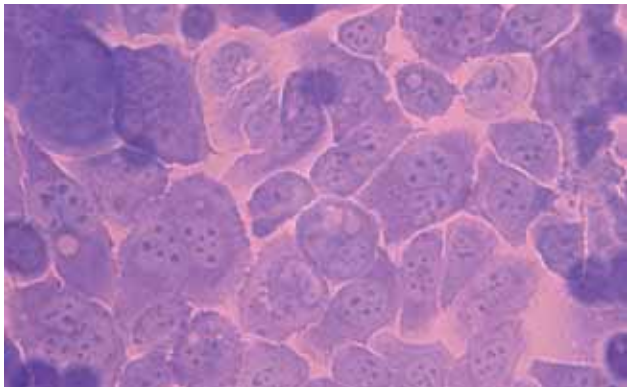
The combination of cDDP and antifolates such as azidothymidine (AZT), a deoxythymidine analogue or, more recently, pemetrexed (Alimta) that inhibits three enzymes in the *de novo* purine and pyrimidine pathways, has been shown to synergistically affect the growth of human ovarian carcinoma cells resistant to cDDP. Due to the role played by the enzymes of DNA synthesis and repair in the occurrence of cDDP-resistance, it seems of great priority to develop clinical reagents designed to limit the intracellular level of TS protein which is associated with clinical resistance, thus sensitising even resistant cells to the effects of anti-cancer drugs. The ultimate aim of LIGHTS is to directly halt tumour progression and interfere with the development of drug resistance upon treatment with platinum-derived drugs by inhibiting the protein regulatory function of TS through small molecule cellular perturbation.

Aim

The project is clearly oriented to directly halt the progression of ovarian cancer and to interfere with the development of drug resistance, upon treatment with platinum-derived drugs, by inhibiting the protein regulatory function of monomeric TS. The intermediate objectives are based on employing novel medicinal chemistry strategies to identify potential drug candidates with new mechanisms of action. LIGHTS specifically addresses early-phase medicinal chemistry issues that can critically influence the time schedule for obtaining an investigational drug candidate. Nevertheless it is also expected as products of our project that potential drug candidate(s) with a high-quality *in vitro* activity profile can be obtained ready for *in vivo* pharmacology profiling.

In particular, LIGHTS objectives are:

- derivation of small-ligand libraries with ligands designed to bind to the thymidylate synthase monomer/monomer interface affecting dimer formation and TS- mRNA interactions;
- validation of the integrated, multidisciplinary drug design strategy necessary to achieve previous objective, which poses a highly challenging design problem. The strategy includes protein cysteine SH-labelling to identify low-affinity ligands, peptide mimetic design, and filtering for ADME properties;
- identification of small-ligands through in a chemical-biology approach as effective perturbing agents to investigate the mechanism of resistance against a panel of cis-platinum-resistant ovarian carcinoma cell-lines;
- development of potential drug candidate(s) with new mechanisms of action for further development as safer therapeutic agent(s) for the treatment of ovarian carcinoma.



Cisplatin-resistant human ovarian carcinoma cells stained with Toluidine blue and observed with a Zeiss axiophot light microscope in a phase contrast mode.

Expected results

The project provides the integration of different scientific areas that are culturally well separated into more established medical approaches to impact health determinant in ovarian cancer disease.

It supports the discovery of new potential anticancer drugs with non-cross resistance profiles; the new potential drug candidate will be ready to enter the pharmacological phase. If the new identified molecules will be moderately/very active with good bioavailability *in vitro* against ovarian cancer, these products will be very interesting to larger pharmacompany and could provide a successful technological transfer outcome.

The proposed research could provide the technical developments and innovation, which could have a large impact on Biotech industry. The selection of the participating SME partners guarantees that the new knowledge (methods, potential drug(s) candidate(s)) might be transformed into new technology and new products.

Potential applications

The proposed research can lead to technical developments and innovation, which could have a large impact on the biotech industry. The selection of the participating SME partners guarantees that the new knowledge – methods and potential drug(s) candidate(s) – will be transformed into new technology and new products. The Consortium, in addition to its contribution to the project's basic research by providing a suitable discovery chemistry programme, will be responsible for further development of the selected promising new chemical entities, comprising intellectual property protection, and chemical and pharmaceutical development.

Project number
LSHC-CT-2006-037852

EC contribution
€ 1 902 150

Duration
36 months

Starting date
01/10/2006

Instrument
STREP – SME

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Keywords | Quality assurance | clinical validation | IMRT | protontherapy | multimodality image registration | virtual simulation software | Monte Carlo dose calculation TPS | *in vivo* dosimeters | risk assessment | accurate patient positioning |

MAESTRO

Methods and Advanced Equipment for Simulation and Treatment in Radiation Oncology

Summary

At the beginning of the third millennium one European citizen out of three will have to deal with a cancer episode in the course of his/her life. Worldwide the estimated number of new cancer cases each year is expected to rise from 10 million in 2000 to 15 million by 2020. Cancer is currently the cause of 12 % of all deaths worldwide.

Within the European Union over 2 million new cancer cases are diagnosed every year and over 1 million people die of cancer. The two leading cause of cancers in Europe are breast and prostate. Therefore combating cancer is a major societal and economic issue for Europe. To face these new challenges strong mobilisation among the scientific community and industrial manufacturers is needed.

Today's approaches to treat cancer are the surgical removal of the tumour tissue, radiotherapy, chemotherapy, and emerging immunotherapy. Among them radiotherapy remains a major technique to treat cancer. More than a half of all cancer patients are treated by radiation therapy thanks to the technical progress made with irradiation equipment in the last years. For external radiation therapy (RT), high-energy photon or electron beams are mainly produced by linear accelerators, for internal radiation therapy or 'brachytherapy', radioactive sources are put in the tumour with undeniable advantages for the patient in given situations.

Problem

Radiotherapy – on its own or combined with chemotherapy – is involved in almost half of the curative cancer treatments of loco-regional type. An even higher percentage of patients could be cured if further improvements of loco-regional treatments involving radiotherapy could be achieved. Such improvements of radiotherapy are the main objective of this project.

Aim

The present project, MAESTRO, proposes innovative research to develop and validate in clinical conditions the advanced methods and equipment needed in cancer treatment for new modalities in high conformal external radiotherapy employing electrons, photons and protons beams.

The project aims at improving the conformation of the dose delivered to the target (tumoural tissues) whatever its shape in order to spare the surrounding tissues. To do this new technologies in the field of patient positionning and organ tracking, advanced software for treatment planning system, dose calculation and measurement, are to be developed, and linked to the emerging IMRT (Intensity-Modulated Radiation Therapy) technique.

MAESTRO incorporates major research and technological development programmes involving clinics and manufacturers which will be linked throughout. The project includes four work packages on research and development activities and two work packages of training and management activities:

- adaptive radiation delivery, tracking and control for radiotherapy (WP1);
- radiotherapy software development (WP2);
- sensors for dose evaluation in radiotherapy (WP3);
- clinical requirements, protocols and validation (WP4);
- organs at risk assessment studies (WP4);
- clinical workshops for training and dissemination purposes (WP5);
- management (WP6).

Expected results

The project has the potential to accelerate development of advanced devices, to ensure their dissemination, to increase the compromise between treatment efficiency and patient safety, to consolidate collaboration between European teams and to spread new methods and knowledge through workshops.

A major expected result of the project is to decrease the number of deaths due to primary tumours without metastases.

Potential applications

Advanced and optimised equipment for innovative treatment approaches for external radiotherapy.

Project number
LSHC-CT-2004-503564

EC contribution
€ 7 000 000

Duration
60 months

Starting date
01/05/2004

Instrument
IP

Project website
www.maestro-research.org

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Keywords | Circadian | clocks | cell cycle | cancer | chronotherapeutics | drug delivery | dynamic models | personalized medicine | chronobiology | pharmacology | anticancer drugs | topoisomerase | cyclin dependent kinases | mouse | patients | transcriptome | proteome | phenome | drug development | systems biology |

TEMPO

Temporal genomics for tailored chronotherapeutics

Summary

Chronic diseases account for 75 % of the disability-adjusted years in Europe and cause the premature death of 17 million people worldwide. Differences in aetiology as well as patient genetic origin, gender, age, lifestyle and biological time structure account for large variability in individual time courses of the same disease entity. Patient-tailored therapeutics is needed to prevent adverse events and improve overall therapeutic activity.

Rather than using pharmacogenomics for excluding patients from an active treatment option, TEMPO will combine functional genomics, proteomics, cell signalling, systems biology and pharmacokinetics to optimize therapeutic index in most individual patients. Thus TEMPO will determine 3 to 5 chronotherapeutics schedules with distinct temporal delivery patterns of the same anticancer drug. Each schedule is adjusted to a different dynamic class of temporal genomics and phenomics parameters related to interwoven circadian and cell division cycles and drug metabolism. *In vivo, in vitro* and *in silico* approaches are integrated through the multidisciplinary excellence in the consortium.

TEMPO will offer a proof of principle of tailored chronotherapeutics in mouse models for irinotecan, an active drug against colorectal cancers, and for seliciclib, currently in clinical testing. TEMPO will gather the corresponding human prerequisites and technology for subsequent application to patients.

Three SMEs play a pivotal role for the impact of TEMPO on European health, economics and society. Novel and complementary *in silico* dynamic models of coordinated clock, cell cycle and pharmacology pathways will identify new therapeutic targets and delivery schedules of active molecules, thus improve drug development processes. New tools will enable personalized medicine to integrate the time dimension in routine implementation.

TEMPO will reduce both therapeutic variability and attrition rates two major impediments for human health and pharmaceutical industries. However time can differ between individuals as a result of genetic polymorphism and lifestyle differences. These determinants can then result in distinct optimal delivery patterns of cancer medication.

Problem

Non communicable chronic diseases represent the bulk of morbidity, disability and premature deaths in Europe and account for 75 % of the disability-adjusted life years. Among these, cancer represents the second cause of morbidity and mortality worldwide. Differences in the molecular characteristics of the tumor cells as well as differences in patient genetic origin, gender, age, lifestyle and circadian rhythms account for large variability in the time courses of cancer diseases and treatment response.

TEMPO addresses the control of several key dynamic pathways in cancer drug metabolism and cellular proliferation by the circadian timing system. This biological system consists of a network of molecular clocks that times bodily and cellular functions along the 24 hours. Chronotherapeutics aim at the delivery of medications according to the 24-hour rhythms generated by the patient's molecular clocks in order both to prevent adverse events and to improve overall therapeutic activity.

Aim

The general objective of TEMPO is to design mouse and *in silico* models reflecting different dynamic classes that predict for distinct optimal chronotherapeutic delivery patterns of anticancer drugs.

Dynamic classes result from the identification of the most discriminant parameters reflecting cell cycle, pharmacology and physiology determinants that are controlled by the circadian clock thus impact on the temporal pattern in drug cytotoxicity. Optimal chronotherapeutic schedule can differ in mice from different strains or housed in different environmental conditions as well as in cancer patients with different gender and circadian timing status. TEMPO will provide a classification based on functional genomics, proteomics and phenomics markers to be selected and validated along the development of the project.

TEMPO will offer a proof of concept of tailored chronotherapeutics with a topoisomerase I inhibitor, and, a cyclin-dependent kinase inhibitor.

The clinical relevance of the dynamic classes established in mice and *in silico* will be continuously reassessed along the development of the project, so as to also identify their counterpart in patients with corresponding specification of optimal treatment delivery profiles.

Primary emphasis will be put on the applications of TEMPO findings to colorectal cancer. This disease affects 300 000 new persons in Europe each year and constitutes the second cause of deaths from cancer in both sexes.

Project number
LSHG-CT-2006-037543

EC contribution
€ 2 086 720

Duration
36 months

Starting date
01/10/2006

Instrument
STREP

Project website
www.chrono-tempo.org

Dedicated experimental models addressing circadian clock, cell cycle and drug pharmacology issues will allow to dissect the molecular and signalling mechanisms that underlie optimal therapeutic schedules for both agents. Dedicated mathematical and computational methods will address complex dynamic issues in chronotherapeutics delivery modelling, based on already existing computational models for the mammalian circadian clock, the cell division cycle and anticancer drug pharmacology.

Expected results

TEMPO combines functional genomics, proteomics, cell signalling, systems biology and pharmacokinetics to optimize therapeutic index in patients. TEMPO will determine chronotherapeutics schedules with distinct temporal delivery patterns of the same anticancer drug. Each schedule is adjusted to a different dynamic class of temporal genomics and phenomics parameters related to interwoven circadian and cell division cycles and drug metabolism. *In vivo, in vitro* and *in silico* approaches are integrated through the multidisciplinary excellence in the consortium.

TEMPO will offer a proof of principle of tailored chronotherapeutics in mouse models for an active drugs against colorectal cancers.

In silico dynamic models of coordinated clock, cell cycle and pharmacology pathways will identify new therapeutic targets and delivery schedules of active molecules. TEMPO will provide tools to reduce both therapeutic variability and attrition rates. New tools will enable personalized medicine to integrate the time dimension in routine implementation.

Potential applications

TEMPO will give the clues to implement research results into clinical applications. Through the identification of nodal points in the interplay between the circadian timing system, the cell division cycle and drug pharmacology determinants, TEMPO will provide key information for potential targeted drug developments.

TEMPO allows foreseeing a new opportunity for cost-effective medical progress through the real development of ambulatory medicine with direct relevance to the quality of life of cancer patients.

The reduction of side effects and the improvement of anti-tumour activity is particularly important in women and in elderly patients who experience nearly 20% more side effects from chemotherapy than men or younger adults.

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Keywords | Anticancer therapy | oncology | health sciences | virotherapy | pox- | myxoma- | adenovirus | colorectal | pancreatic | ovarian cancer | tumour-specific targeting | spreading | replication | arming | molecular chemotherapy | non-invasive imaging |

THERADPOX

Optimised and novel oncolytic adenoviruses and pox viruses in the treatment of cancer: Virotherapy combined with molecular chemotherapy

Summary

Today, cancer is the second cause of disease-induced mortality worldwide. Among the innovative treatments for cancer, virotherapy holds great promise. Virotherapy exploits an intrinsic feature of the life cycle of oncolytic viruses (OVs): replicating and spreading exclusively in tumour cells leading to their destruction, while not affecting normal cells. Clinical studies have demonstrated the safety and feasibility of this approach, but have shown only minimal therapeutic efficacy. Synergistic effects of combination treatments of OVs with chemo- and radiation therapy have been observed. Nevertheless, this approach still leaves patients subjected to the toxic adverse effects of chemotherapy and radiation. Thus, an unmet need exists for the improvement of current and the development of new treatment platforms, leading to a significant increase in cure rates.

Owing to their inherent strong oncolytic potency and safety record, poxvirus and adenovirus-based vectors have been chosen to pursue the goal of the THERADPOX project: to improve the safety and therapeutic efficacy of OVs *in vivo.* Novel and improved OVs will be engineered which, *in vivo*:

- specifically target colorectal, pancreatic and ovarian cancer cells;
- replicate exclusively in cancer cells;
- are armed with therapeutic genes rendering only tumour cells sensitive to chemotherapy;
- widely spread within the tumour to permit total tumour eradication.

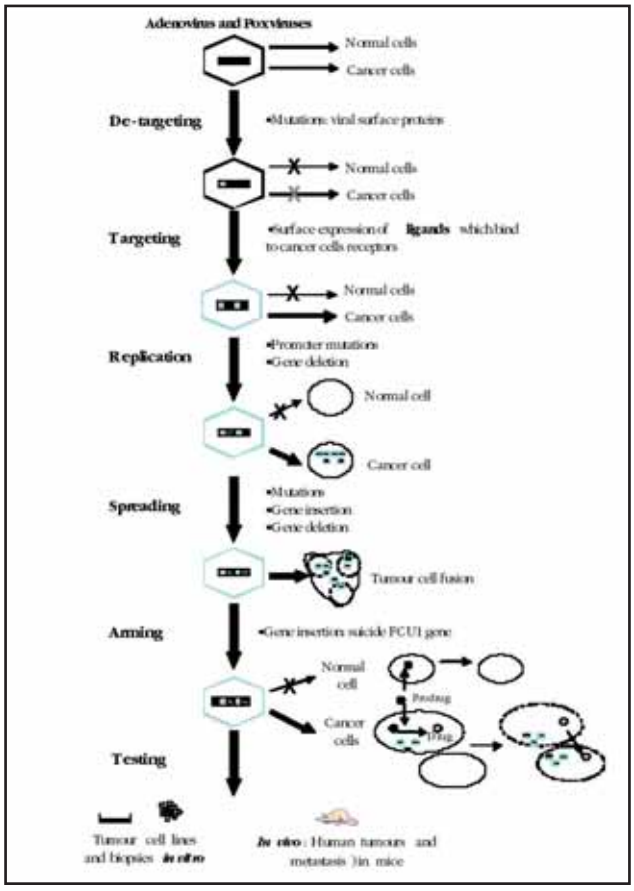
Through the multidisciplinary work plan proposed and the strong and complementary expertise of the ten European partners from five European countries involved, the THERADPOX project will:

- generate advanced knowledge which could be translated towards a safer cancer treatment with an increased therapeutic index;
- contribute to improve the quality of life of cancer patients by fewer treatments with no toxic side effects;
- lead to the proposal of new guidelines and standards for the development of OVs;
- strengthen the competitiveness of Europe in the war against cancer.

Problem

Cancer still remains the second leading cause of death in Europe and in the world. THERADPOX, by providing new treatments for three major (colorectal, pancreatic and ovarian) cancers, will contribute to addressing and pursuing central directions of the European policy against cancer.

Virotherapy exploits the use of natural or engineered Oncolytic Viruses (oncolytic vectors, OVs) to selectively kill tumour cells. To date, many types of OVs have been developed and have entered clinical trials. These trials demonstrated a high safety profile of OVs, but showed limited therapeutic effect when used as a monotherapy. Improved efficacy was noted when OVs were used in combination with traditional therapies (chemotherapy or radiation). However, the efficacy and safety of virotherapy is limited by the low efficiency of tumour cell infection, the low level of replication in some tumour cells and the inefficient spreading capacity within the tumour mass.



THERADPOX approach.

Aim

The THERADPOX project aims at engineering novel and optimised oncolytic pox- and adenoviruses for cancer therapy, specifically targeting colorectal, pancreatic and ovarian cancers. The innovative strategy of THERADPOX relies on the original engineering of OVs to render them safe, specific and efficient for infection (binding and replication) and for the destruction of cancer cells through a combination of virotherapy with non-toxic chemotherapy *in vivo*. To achieve an enhancement of tumour cell infectivity of THERADPOX vectors, tumour-specific ligands, for which particular membrane proteins of cancer cells show high affinity, will be incorporated in viral surface proteins and will be optimised. In addition, by modifying or exchanging ligand expression of THERADPOX OVs, one can imagine targeting other tumour types. The viral genome will also be engineered to ensure that viruses selectively replicate and express therapeutic proteins in tumour cells and that they spread widely through the tumour mass. Furthermore, capsid modified oncolytic Ad vectors will be explored to overcome pre-existing immunity and delay an induced immune response.

The oncolytic vectors (OVs) will be derived from the viral platforms described below:

- vaccinia virus (VV): the advantages of VV as OV are a quick and efficient life cycle, strong lytic activity and rapid cell-to-cell spreading. The virus can infect a wide variety of human tissues but does not cause any known human disease. VV was the first widely used vaccine which resulted in the eradication of smallpox. As a result, the responses, safety profile and adverse reactions have been extensively studied and documented;
- myxoma virus (MV): MV causes myxomatosis in European rabbits but is non-pathogenic in man. However, myxoma virus productively infects a variety of human tumour cells (Sypula et al., 2004), suggesting a significant potential for exploiting MV as a novel OV platform;
- adenovirus (Ad): one of the most extensively studied viruses which have been engineered for gene therapy and for virotherapy of cancer, particularly serotypes 2 (Ad2) and 5 (Ad5). The virus is endemic in the human population and its natural pathogenicity is associated with mild respiratory infections (common cold). It can be grown easily and to high titres, and the methodology to generate recombinant viruses is well established.

Expected results

THERADPOX OVs will be engineered to:

- selectively target cancer cells *in vivo* (up to a 100-fold increase of tumour cell infection can be expected: 100 cancer cells infected for 1 normal cell infected) (M30);
- selectively replicate and propagate in tumour cells *in vivo* (expectations are a 100-fold increase of viral yield in tumour cells versus normal cells) (M32);
- widely spread within tumours *in vivo* (a statistically significant increase of the therapeutic index is expected) (M30);
- specifically render cancer cells sensitive to chemotherapy *in vivo*: OVs will be engineered to express in the infected cancer cells prodrug- converting enzymes, enabling the conversion of a non-toxic molecule (given orally or intravenously) to toxic compounds (a statistically significant increase of the therapeutic index is expected) (M36);
- overcome the pre-existing immunity and to delay the induced adenoviral immune response, concerning oncolytic Ad (M36).

Potential applications

The THERADPOX project contributes to supporting the Programme of Community action in the field of public health (2003-2008) (1786/2002/EC) by:

- promoting and improving health, with a view to reducing avoidable morbidity: THERADPOX will develop new OVs to cure patients affected with colorectal, pancreatic and ovarian cancers;
- reacting rapidly to health threats: THERADPOX vectors are designed to eradicate tumours. Their selectivity for one tumour type relies on the tumour cell selectivity of specific ligands. Thus, by only changing the ligand in THERADPOX OVs, one can imagine targeting and efficiently and rapidly eradicating other tumour types that may be a threat to human health in the future;
- promoting better knowledge and communication flows, thus allowing a greater involvement of individuals in decisions that concern their health. THERADPOX includes specific tasks for:
  - communicating about the knowledge, impacts and benefits of the project;
  - disseminating results and information, in a simple, clear and sound way about the work undertaken within THERADPOX to the scientific community as well as to the community population, with the ultimate goal to improve the quality of life.

Project number
LSHB-CT-2004-018700

EC contribution
€ 2 411 006

Duration
36 months

Starting date
02/11/2005

Project website
www.theradpox.org

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Keywords | Breast cancer | clinical trials | molecular signature |

TRANSBIG

Translating molecular knowledge into early breast cancer management: building on the Breast International Group (BIG) network for improved treatment tailoring

Summary

The key to individualising treatment for cancer lies in finding a way to quickly 'translate' the discoveries about human genetics made by laboratory scientists in recent years into tools that physicians can use to help make decisions about the way they treat patients. This area of medicine that links basic laboratory studies to the treatment of patients is called translational research. TRANSBIG has been created as a multidisciplinary network of excellence, devoted specifically to this type of research in breast cancer.

TRANSBIG is a research network of 40 world-class institutions in 21 countries. Each participating organisation brings with it expertise that ranges from being specialised in cutting-edge biomedical technologies and cancer treatment programmes to lobbying governments on behalf of patient groups and supporting cancer societies. As a network, TRANSBIG will be dedicated to high-level collaboration that will contribute dramatically to advancing individualised treatment for breast cancer patients. Among its many strengths is the fact that it is linked to an already existing network of groups around the world that conduct clinical breast cancer research together – the Breast International Group (BIG). BIG's 44 member organisations are active in 40 countries.

The headquarters is located in Brussels, and it coordinates the activities of both TRANSBIG and BIG. By linking the two networks and by benefiting from a central coordinating body, the fragmentation currently existing in the field will be reduced, and translational research in Europe will be strengthened and accelerated. New technologies will only gain acceptance by physicians and patients after first being validated in large, independent clinical trials. Microarray technology has enabled scientists to determine the signature of individual tumours, but it must be proven that this information is more reliable than existing methods for determining how best to treat individual patients.

Problem

Breast cancer is the most common cancer among women in developed countries, with one out of eight to ten women developing the disease in her lifetime. While incidence has steadily increased over the past decades, a slight decrease in deaths from breast cancer has only recently been noted, and that only in a few countries. Breast cancer is curable in about 70% of cases if diagnosed and treated early enough. But because of uncertainty over the best treatment in individual cases, many women receive chemotherapy or hormonal treatment after surgery, based on the assumption that there is a high risk of their breast cancer recurring. Some women benefit significantly from such treatment, others only very little or not at all. The reason for this is because breast cancer is a disease that develops very differently in each woman. If individual tumours were better understood, physicians would be able to make more enhanced decisions about which treatments are best for individual patients and which patients need no further treatment after surgery. Presently it is estimated that about 12 to 20% of patients are over-treated, resulting in avoidable costs to both health services (financial) and patients (side-effects).

Aim

The aims of this network are:

- to develop ways of individualising breast cancer treatment, so that treatment is tailored to the person receiving it;
- to integrate, strengthen and facilitate translational clinical breast cancer research in Europe and internationally by linking it to an existing network for clinical breast cancer trials (BIG);
- to develop and run a major clinical trial aimed at validating the hypothesis that understanding the genetic make-up (signature) of a tumour can lead to better targeted treatment.

Although TRANSBIG will ultimately develop many projects, it will start with a clinical trial called MINDACT (Microarray for Node Negative Disease may Avoid Chemotherapy). This trial will compare two different ways of assessing the probability or risk that a woman's breast cancer will come back. The traditional method is based on international guidelines and looks at specific characteristics such as the size of a patient's tumour and whether the disease has spread to the lymph glands (nodes).The new method uses microarrays as a way of analysing the genetic components of a tumour. Specifically, traditional methods of assessing risk will be compared to a 70-gene tumour 'signature' identified by a group of scientists at the Netherlands Cancer Institute that appears to predict very accurately whether a particular woman's breast cancer will come back. MINDACT will involve

6 000 women over a three-year period. Other cutting-edge techniques and technologies will be used in the project over time, and tumour and blood samples donated by patients will create an invaluable resource for further research that will help us to better understand and treat breast cancer.

Expected results

The TRANSBIG partners believe that the results of MINDACT will show that using the new technology to assess risk will result in fewer women being treated unnecessarily. This, in turn, will mean that fewer women will suffer from the unpleasant side-effects of chemotherapy. Not only will the overall quality of life of breast cancer patients be improved, but the healthcare costs associated with such cancer treatment will be reduced as well, thus providing a significant benefit to society. As the first project in TRANSBIG, MINDACT will also establish valuable resources for future research and establish links between research and biotechnology enterprises in order to develop further diagnostic tools that can be widely disseminated and easily used by scientists and physicians alike.

Potential applications

The long-term aim is to develop TRANSBIG into a permanent network for translational research that is complementary to the clinical work done by BIG. This guarantees a connection between what scientists learn in the laboratory and what physicians and patients decide together about treatments in the clinic. But TRANSBIG's reach will be wider than simply research. It will also be concerned with education through the provision of traineeships for young scientists and physicians, and public education on the issues involved with genomics by working closely together with cancer societies and patient advocacy groups. By bringing together scientists, clinicians, and representatives from patient groups, cancer societies and industry, TRANSBIG will bring a coherence and synergy to breast cancer research that has previously not existed in Europe.

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TRIDENT

Therapeutic molecules for treatment of solid tumours by modulating death receptor-mediated apoptosis

Summary

The efficacy of current treatments for some types of solid tumours is disappointingly poor. New therapies using novel tumour-selective anti-cancer agents are necessary. A major aim of anti-tumour therapies is to inhibit proliferation and induce death of tumour cells without affecting normal cells. In this regard, members of TNF ligand/receptor family are of interest since they regulate both apoptosis (programmed cell death) and cell proliferation. One TNF family member, TRAIL, is of particular interest since it selectively induces death of tumour cells without affecting normal cells. Currently, TRAIL and TRAIL-specific antibodies are being investigated as anti-cancer agents. However, a major drawback to TRAIL's efficacy is that it binds to multiple receptors, not all of which transduce an apoptotic signal. Previously, we developed receptor-selective TRAIL variants which are potent inducers of apoptosis in various tumour cells, are more efficacious than native TRAIL, and display synergistic effect in combination with other chemotherapy treatments or radiotherapy.

This proposal will investigate and characterise TRAIL variants pre-clinically in solid tumour models and define new treatment protocols in combination with already proven treatments. Furthermore, we will elucidate the role of other TNF receptor family members in signalling in tumour cell survival/death. Biochemical and structural characterisation will identify new targets for molecular cancer therapy while computational design and molecular evolution techniques will be used to develop novel receptor-selective apoptosis-inducing agonists. We will also develop intracellular acting agents (intracellular-acting peptides inhibiting pro-survival signals; intracellular peptide inhibitors), which will block the unwanted proliferative/anti-apoptotic signals activated by some TNF members. The tumoricidal activity of these lead molecules will be tested using conventional, viral and cell based delivery strategies which will utilise peptide sequences to specifically target them to tumour cells.

Problem

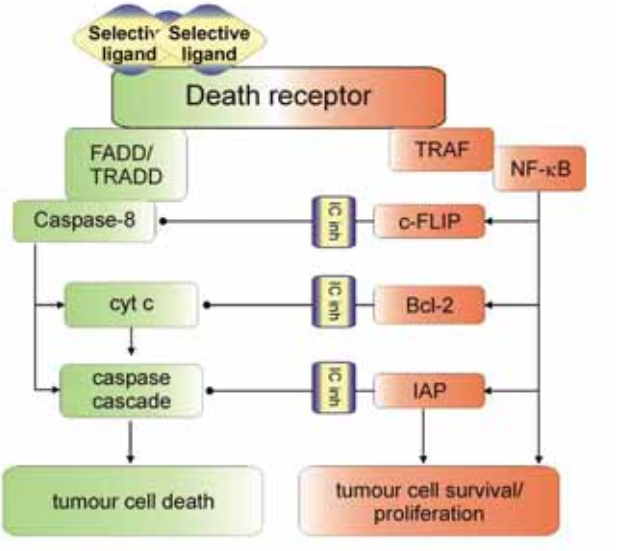
With almost 3 million new cases each year and 1.7 million deaths, cancer is an important public health problem in Europe. The ageing of the European population will cause these numbers to continue to increase. The most common cancers are lung, colorectal and breast cancers. The available treatments for these solid cancers and the outcome of the treatments are not satisfactory. New therapeutic strategies and novel tumour-selective anti-cancer agents are necessary in order to improve the treatment of these and other solid tumours.

Aim

The ultimate aim of the TRIDENT project is to develop novel molecules that target critical apoptotic signalling pathways important in the formation of various solid tumours.

The specific objectives are:

- to develop of novel apoptosis-inducing agonists and proliferation antagonists using state-of-the art, computer based rational design and directed evolution techniques;
- to gain in-depth knowledge on the role of the TNF ligand-receptor family interactions in the carcinogenesis of solid tumours, both at a molecular and structural level;



The objective of TRIDENT is to channel death receptor activation towards tumour cell apoptosis. Activation of cell surface death receptors do not only induce apoptosis of the receptor carrying cell but can simultaneously activate compensatory, pro-survival pathways, which limits the use of this pathway to kill cancerous cells. The TRIDENT project aims to generate TNF ligand variants that only bind to the death-inducing members of the TNF receptor family, not to decoy TNF receptors (selective ligand) and design cell permeable peptide inhibitors (intracellular inhibitors; IC inh) against anti-apoptotic molecules. These novel molecules used in combination can maximize tumour cell killing.

- identify high efficiency combinations of the novel lead molecules with chemotherapy and/or radiation and conduct pre-clinical studies;
- develop a prediction model and high-throughput primary tumour characterisation to identify patient-specific (tailor-made) targeted treatments;
- devise new tumour targeting techniques by exploiting gene and cell therapy-based approaches;
- development of new computational and experimental methods in order to advance potential protein therapeutics faster from pre-clinical to clinical stage;
- development of an exploitation strategy involving a start-up SME.

Expected results

The anticipated deliverables include the development of novel diagnosis technologies and novel therapeutics for intervention in cancer progression through activation of apoptosis as well as technologies to advance a more rational approach to the design of 'tailor-made' therapeutic drugs. This proposal takes a multi-disciplinary approach to develop new methodologies and will specifically generate unique scientific knowledge and industrial technologies that could not be created on a national level by individual partners. The participants involved are from both industrial and academic backgrounds and are experienced with working in research networks at a European level. Our application of state-of-the-art technologies will facilitate and accelerate the development of new tools and processes in general, for development and production of novel protein/peptide therapeutics.

TRIDENT will assist in the advancement of genetic and protein engineering, *in silico* protein design, molecular evolution, protein microarray technology and lab-on-a-chip formats in the development and production of lead therapeutic molecules. A greater understanding of molecular mechanisms involved in the control of apoptotic signal transduction in tumour cells will be also gained. The integration of this derived knowledge will ultimately be useful in the context of post-genomic research for human health activities. Our focus will be on the market need for alternative, more effective therapies in the treatment of solid tumours, and more particularly for therapeutics with minimal toxic-side effects.

Potential applications

Treatment of solid tumours and possibly leukemias, identification of most efficient treatments for individual patients, high efficiency design of protein mutants and specialised-variants (e.g. receptor selective ligands, agonistic, antagonistic ligands).

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STREP

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Keywords | Lymphoma | leukaemia | vaccine | idiotype | immunotherapy |

VITAL

Development of optimised recombinant idiotypic vaccines for subset-specific immunotherapy of B cell lymphomas

Summary

Therapeutic vaccines targeting B cell non-Hodgkin lymphoma (NHL) idiotype (Id) represent a promising approach against these malignancies. A broad use of Id-based vaccination, however, is hampered by the complexity and costs due to the individualised production of these vaccines. Recent evidence indicates that these limitations may be overcome. In fact, distinct sets of stereotyped immunoglobulins have been identified in various B-NHL, suggesting that patients share Id with a higher frequency than appreciated previously.

Through the complementary and synergistic work of academic partners and three SMEs, we plan to exploit the molecular features of Id proteins of distinct B cell lymphomas/leukemias, particularly those pathogenically associated with antigen stimulation and/or selection, to develop pre-made, recombinant Id proteins to vaccinate subgroups of lympho-proliferative disorders expressing molecularly correlated idiotypes.

A database of Id sequences expressed by different B-NHL will be constructed to identify subgroups of tumours expressing molecularly correlated Id proteins. Selected Id proteins will be characterised for their immunogenicity and, particularly, for the ability to induce cross-reactive immune responses against related Id proteins. B and T cell epitopes will be identified using innovative approaches, and dedicated assays for immunomonitoring will be developed. Optimised versions of selected Id vaccines will be produced using new strategies and validated in animal models. New adjuvants and delivery systems for improved Id vaccine formulations and administration will be also evaluated and validated. The most promising Id proteins will be produced and purified according to GMP standards and included in new vaccine formulations for innovative trials of 'cross-reactive' immunotherapy.

Problem

Non-Hodgkin's lymphomas (NHL) constitute a heterogeneous group of malignancies whose incidence has significantly increased in recent decades. In the year 2000, more than 145 000 cases of NHL were diagnosed in developed countries, representing the sixth most common cancer occurring among men and the eighth among women. Low-grade B cell NHLs, in particular, are incurable diseases characterised by relatively slow growth and excellent initial responsiveness to chemotherapy but also by continuous relapses. In particular, for patients with follicular lymphoma, median overall survival (7-10 years) has not improved over the past 30 years.

Although in the vast majority of patients complete or partial remissions can be obtained with either single agents or combination chemotherapy, the clinical course is characterised by a high relapse rate. After relapse, both the response rate and relapse-free survival after subsequent salvage treatment regimens steadily decrease, resulting in a median survival of only 4-5 years after the first relapse. These clinical findings, coupled with the substantial toxicities of standard treatments, have stimulated the search for novel and more tumour-selective therapies. Therapeutic vaccines targeting B cell lymphoma idiotype (Id) represent a promising immunotherapeutic approach for a better clinical control of these malignancies. This strategy is based on the observation that immunoglobulins (Ig) expressed by neoplastic B lymphocytes carry unique determinants in their variable regions (idiotypes), which can be recognised as tumour-specific antigens.

Indeed, both protein- and dendritic cell-based vaccines that use the patient-specific Id have resulted in clinically significant tumour-specific cellular responses with very little toxicity. A broad use of Id-based vaccination for B cell lymphomas, however, is hampered by the fact that these approaches are patient-specific, so that the vaccine must be individually produced for each patient. On these grounds, new strategies obviating the need to produce customised vaccines would further simplify clinical applications of idiotypic vaccines.

Aim

The objective of VITAL is the development and production of optimised recombinant idiotypic vaccines for the treatment of subgroups of lymphoproliferative disorders expressing molecularly correlated idiotypes. These vaccines will be included in new formulations for innovative trials of immunotherapy potentially targeting a large fraction of lymphoma/leukemia patients.

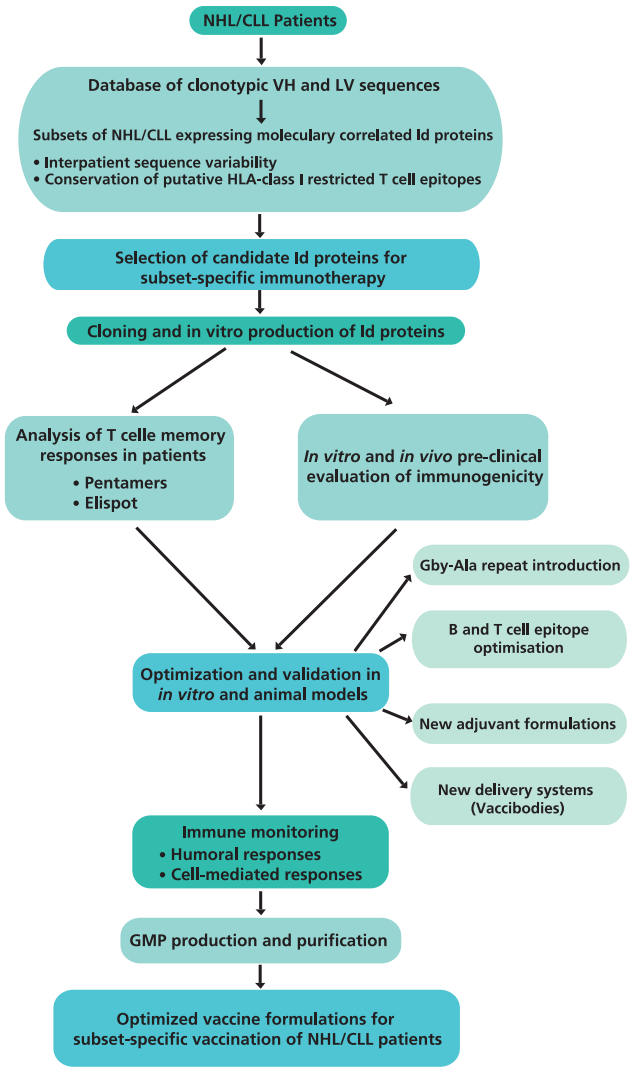
Expected results

- Establishment of a large database including sequences of idiotypic VH and VL genes expressed by a variety of lympho-proliferative disorders, including low grade B-NHL, autoimmunity-associated lympho-proliferations, and chronic lymphocytic leukemia. This will allow the identification of candidate Id proteins for 'cross-reactive' immunotherapy.
- Pre-clinical characterisation of the immunogenicity of selected natural Id proteins, with particular regard to their ability to induce immune responses against lymphoma cells expressing molecularly correlated Id proteins. The characterisation will include the identification of B cell epitopes and HLA Class I-restricted cytotoxic T cell epitopes using innovative approaches and will allow the development of dedicated assays for immunomonitoring.
- Design and validation of optimised Id vaccines.
- Evaluation and validation of new adjuvants and innovative delivery systems for improved Id vaccine formulations and administration.
- 'Clinical-grade' production and purification of optimised Id proteins for patient vaccination.

The SMEs are an integral part in the project in making the new diagnostic and therapeutic tools available, not only for Europe but also for the world market. The close integration between clinical and research activities at several university hospitals and cancer centres with the SMEs will form new centres of excellence where European SMEs will benefit from close collaboration, at the same time as new diagnostic and therapeutic products will be developed to the benefit of patients with lymphoid malignancies.

Potential applications

The results obtained in the present project will allow the design and activation of phase I/II clinical trials aimed at validating the use of optimised, pre-made vaccines for the treatment of a relatively broad spectrum of lymphoid malignancies. The proposed Id vaccination may be beneficial also for patients with pre-neoplastic B-cell lymphoproliferations, such as mixed cryoglobulinaemia. These vaccines, in fact, may be used with the purpose of alleviating symptoms and, ultimately, preventing a possible evolution towards an overt B cell malignancy. Once validated as drugs, the vaccines will have the advantage of being easily distributed to all hematology and oncology departments, including those of peripheral hospitals/universities. Thus, results obtained in the present project will have an important strategic impact in solving, at least in part, the dramatic social and health problem represented by NHL.



Flow chart, outlining the main expected results, leading from identification of shared idiotypes to the development of optimized vaccines for the treatment of B-cell lymphoproliferations.

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www.cro.sanita.fvg.it/progetti/vital/index.htm

Cancer control, Survivorship and outcomes research

The projects included in this part of the catalogue have a particular importance in controlling cancer and although they belong to different scientific areas, their contribution to the portfolio is important. The first group of projects belongs to what could be called analysis of funding provision in research, proposals to enhance quality of the funders and surveillance. The CCRB project aims to improve cancer control by linking biobanks and cancer registries through integration activities; EUROCAN +PLUS, a coordination activity of the European research area (ERA), is trying to identify research where national coordination is lacking and whether there is a possibility to achieve better coordination. EUSTIR, although a smaller scale project than the ones previously mentioned, has an equally important objective to propose harmonisation activities in breast cancer research funding bodies in order to achieve better research results and to be able to control breast cancer research more effectively.
Quality of life, pain control and management and psychological impact of cancer patients – in short palliative medicine and care – incorporates in a complex disease such as cancer, which is often incurable, a continous input from the start of the disease to the end of life care for the patients, their family and care givers.
This area of research of growing importance receives special attention among funding and policy makers in cancer research.
There are two projects representing this area of research: NORMOLIFE which is aiming to synthesise new compounds alternative to opioids, to fight pain and reduce side effects; EPCRC is an ambitious project aiming to identify the genetic variation to opioid responses and cachexia, to improve the classification of pain, depression and cachexia and most importantly to develop guidelines for the above symptoms.

Elengo Manoussaki

Keywords | Biobank | registries | population-based | standards | harmonisation | quality assurance | genetic epidemiology | infections |

CCPRB

Cancer Control using Population-based Registries and Biobanks

Summary

This Network of Excellence project is aimed at improved control of cancer by facilitating research linking bio banks and cancer registries. The project involves a systematic quality assurance of European bio banks, as well as improved integrity-protection in the handling of sensitive information in connection with bio bank-based research. The samples in the biobanks will be used in large-scale cancer research searching for genetic and infectious causes to cancer, particularly in the areas of breast and colorectal cancer, and childhood leukaemias.

Problem

Longitudinal studies nested in biobanks enable more reliable and efficient study designs, for both design and evaluation of cancer treatment and cancer prevention, as well as for exploring and evaluating etiologic hypotheses. However, several prerequisites apply:

- there must be very large-scale biobanks in place that should already have information dating back several decades;
- it must be possible to link biobanks with quality-assured, population-based cancer registries to enable population-representative studies with minimal case ascertainment bias;
- important problems regarding overview, accessibility, quality control, phenotypic characterisation, efficiency and avoiding risks for violation of personal integrity must be addressed.

Aim

The objective is to achieve improved control of cancer by facilitating research that links biobanks and cancer registries.

Expected results

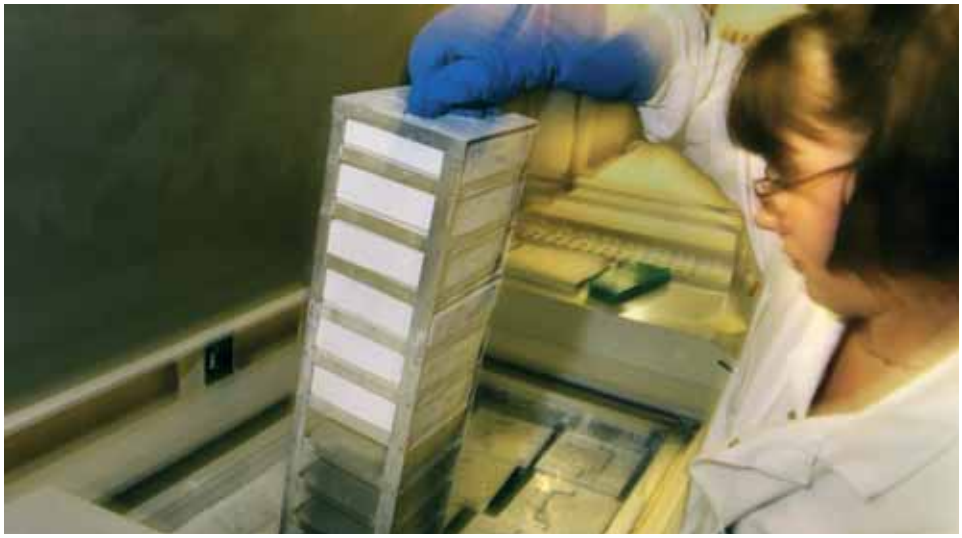
- Provide the study base for uniquely large population-based prospective studies on cancer.
- Define and implement a European Quality Standard for Biobanking.
- Define and promote the implementation of integrity-proof methods for biobank-based research involving well-defined and secure thirdparty code-keeping systems.
- Establish a Europe-wide network for spreading the awareness of possibilities and best practice quality standards for biobank-based research.

Potential applications

Large-scale, population-based research will be enabled on:

- evaluation of cancer treatment and role of molecular markers in treatment selection;
- identification and evaluation of genetic markers associated with increased cancer risk using over-generation linkages;
- exploration and evaluation of intrauterine exposures associated with increased cancer risk using over-generation linkages;
- design of optimal strategies for cancer prevention and its evaluation.

The samples in the prospective research biobanks are allocated into colour-coded tubes (buffy coat, EDTA-plasma, heparin-plasma, etc.).



Work in the -80 ° facility in the Malmö Biobank Consortium.

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Keywords | Cancer | palliative care | pain | depression | fatigue | cachexia | opioid response | genetic marker | classification | assessment | guidelines |

EPCRC

The European Palliative Care Research Collaborative: improved treatment of pain, depression and fatigue through translation research

Summary

Pain, depression and fatigue are subjective clinical manifestations of advanced cancer. Control of these symptoms is pivotal for the quality of life of millions of palliative care patients. Pain is the most feared symptom for many patients. The prevalence of depression varies from 6-58 % in palliative care patients, reflecting lack of a standardised validated methodology for its assessment in these patients.

Cachexia is likely to be the most important contributor to fatigue in palliative care. The plethora of other symptoms, co-morbidities, and the advanced age of most palliative patients support the need for evidence-based management strategies. To improve management of pain, depression and cachexia in cancer patients demands new knowledge through research in several areas.

The research plan of the EPCRC will be based upon questions raised in a clinical setting, with focus on palliative care cancer patients, thus a 'true' translational approach is chosen. The research will focus both on diagnosis and classification of these symptoms and on an understanding of the underlying mechanisms. To reach the aims of EPCRC requires a multidisciplinary approach, including basic scientists and clinicians who will translate human genome data into practical applications for these patients.

Assessment and classification of pain, depression and cachexia (fatigue) are the basis for diagnosis and subsequent treatment. By use of modern molecular biology methods in this project, we will increase the understanding of the role of genetic variability for pain and cachexia. European evidence-based Internet guidelines will be developed by members of the EPCRC, supported by an international advisory board. By recruiting a pan-European panel, cultural, social and language barriers will be taken into consideration in the early phase of guideline development.

Problem

Even though pain, fatigue and depressive symptoms are the most common symptoms in advanced cancer, there is still inadequate understanding of the inter-individual variability of these problems. Cachexia is a major reason for fatigue in palliative care patients, but there is no internationally agreed assessment tool or classification system for either cachexia or depression in this patient group. Although there are several publications and agreements on the classification of pain, there is still no consensus on how to assess or measure it. In addition, there is a lack of internationally developed and updated clinical guidelines for the treatment of these conditions and symptoms.

Aim

The overall objectives are to develop novel genetic methods for prediction of opioid responses and individual variation of fatigue (cachexia), and methods for assessment and classification of pain, fatigue (cachexia), and depression.

- To identify genes and genetic variation relevant for inter-individual variation in opioid responses and genetic variation that may identify patients at particular risk for developing cachexia.
- To improve classification and assessment of pain, depression and cachexia by computer-assisted approaches.
- To combine the new knowledge of symptoms, genomics and assessment in an Internet-based system for implementation of European evidence-based guidelines, which will include standardised assessment and individualised treatment plans for pain, depression and cachexia.
- To develop a long lasting European Collaborative in palliative care cancer research.

Identification of profiles of genetic markers that best predict pain treatment responses.

Project number
LSHC-CT-2006-037777

EC contribution
€ 2 799 910

Duration
36 months

Starting date
01/11/2006

Instrument
STREP

Project website
www.EPCRC.org

Expected results

- Identification of profiles of genetic markers that best predict pain treatment responses, with specific emphasis on opioids.
- Increased understanding of the molecular basis for cachexia and identification of genetic factors that may predict patients at particular risk.
- Increased understanding of the value of serum parameters as an indicator of pain response.
- Better methods for classification and assessment of pain, depression and cachexia in palliative care.
- International European-adopted and agreed clinical guidelines for classification, assessment and treatment of pain, depression and cachexia in palliative care.
- Guidelines available and regularly updated on the EPCRC website, the EAPC (European Association for Palliative Care) website, and other relevant websites.
- Guidelines translated and disseminated in relevant European languages.

Potential applications

The aim of the EPCRC is to have the guidelines disseminated and universally accepted within the palliative care community in Europe, both in clinical work and research.

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Keywords | Collaboration | article 169 | research priorities | quality control | survival | prevention | clinical trials | translational research |

EUROCAN+PLUS

Feasibility Study for Coordination of National Cancer Research Activities

Summary

A key issue remains how effective coordination of Cancer Research in Europe can see the European Union (EU) benefit from the advantage of scale, which its population provides. Cancer research in EU is fragmented and frequently duplicative. Resources are wasted and implementation of closer cooperation to develop a strategy for Cancer Research by the Member States would clearly be cost-efficient and hasten the development of major advances and their delivery to the population. Barriers to collaboration in cancer research need to be identified and ways sought to encourage the development of collaborations in the Member States.

Problem

Cancer remains a major Public Health problem worldwide with Europe hit hard and the situation set to worsen in absolute terms as the population ages. Around one half of cancer patients still die from their disease. On the other hand, there are currently great expectations that we are on the brink of making huge progress against the disease. Elucidation of the human genome and rapid advances in understanding details of its function allied to rapid progress in technology, gives great hope of rapid advances taking place. The current era offers more real hope than any previous.

Cancer remains the subject of significant research effort at both the European level and in the Member States. Between 2002 and 2006, the European Union will be devoting more than €435 million to this field of research. This is in addition to national funding in Member States.

An important aim for the Commission is to achieve a better framework for collaboration in cancer research in Europe, and there is a recognition that coordination of national cancer research efforts at the European level is far from being achieved. Among the key elements proposed to explain this situation are the barriers between disciplines and fields of research; the fragmentation of research activities dedicated to the different types of cancer and the resultant sub-optimal critical mass; the weakness of the links between basic, applied and clinical research, leading to a rather limited integration of basic and clinical research; and the implementation of all these activities mainly in a national framework and a national context. As a consequence, Europe is unable to fully benefit from the advantage of scale afforded by its 500 million population.

Europe is at present, and has been for many years, unable to retain many of its most talented scientists and is unable to provide a scientific environment capable of attracting top young scientists from outwith the continent. In addition, there is no national incentive to promote mobility within the Member States. Consequently, the development of transnational research activities is impeded by the obstacles to the mobility of researchers.

A further obstacle is the lack of common core elements in the curriculum of professionals. Common quality standards in training are needed to facilitate the collaboration at European level as well as the mutual recognition of the qualifications between European countries and therefore the mobility of researchers and physicians. The situation is particularly exemplified by the absence of recognition of Oncology as a Medical discipline by many European countries and its variable status in most Member States.

Consequently, although a large amount of financial resources is involved, and a substantial portfolio of initiatives is carried out, cancer research efforts are not currently benefiting from the advantages that a coherent and more co-ordinated framework would bring about.

Aim

On the basis of an overview as complete as possible of Cancer research in Europe, objectives of the project are to:

- identify the fields, topics and research subjects where the lack of co-ordination of national activities is particularly detrimental for the progress of knowledge and the quality of care;
- identify those specific fields, topics and research subjects where the awareness of the need, as well as the willingness and readiness to achieve a better co-ordination, are established enough as to make such an achievement likely;
- explore the suitability, for this purpose, of the various support schemes available in the Sixth Framework Programme (Coordination actions; ERA-NET schemes; article 169);
- explore, in particular, the interest and feasibility of an initiative based on article 169 (participation of the EU into national research programmes jointly implemented);
- help determine the means by which further exploring the possibilities and ways to progress in the direction of a better coordination (study, workshop, conference, survey);
- give orientation on all the issues above raised and practical recommendations on the last points.

Project number
LSSC-CT-2005-015197

EC contribution
€ 3 000 000

Duration
24 months

Starting date
01/10/2005

Instrument
SSA

Expected results

The project shall provide key answers to the following questions through the exploration of barriers to Research Collaboration in the EU in specific fields as well as by dealing with some of the key issues including mobility of cancer research workers throughout the European Union:

- irrespective of the prospects generated by considerations of alternative legal, governance and financial matters, including article 169, what can be done to facilitate Cancer Research in the European Research Area?
- what could be done to enhance Cancer Research in the European Research Area by new application(s) of available legal, governance and financial considerations, including article 169?

Potential applications

The project is certainly going to have a major impact on the structure of Cancer Research, basic and clinical, throughout the EU. Furthermore, the EU will dispose of concrete and practical recommendations for the definition of priorities in research programmes.

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Keywords | Breast cancer | funding | harmonisation |

EUSTIR

A European strategy for the integration of research on breast cancer

Summary

The overall objective is to create a permanent European overview process for the award, audit and recording of all research on breast cancer.

The project aims to create:

- a European overview process for project proposals received by all funding bodies. This will:
  - prevent research from being funded for similar work in multiple projects;
  - result in a few large, rather than multiple small series, which are much more likely to yield definite results;
- a body of the leading researchers in breast cancer which agree the areas most likely to give results of clinical relevance and agree certain issues that must be included in all proposals (such as validation of the results);
- an audit process of research work. This addresses the problem that many projects do not address their aims. The audit outcomes will be accessible to research funders, so that institutes most likely to complete valuable projects are identified (and the converse!).

This project will be divided into three parts:

- a workshop of leading European research workers in breast cancer to define the most important areas for research and to make suggestions on an overview process;
- a workshop of the funding organisations and other interested parties to discuss and agree a strategy for harmonising research in the identified areas;
- validation of projects funded to date against criteria established within the project.

Problem

The present methods of awarding research grants in cancer suffer from many defects and appear to result in repetitive research, often with no clear result and no clinical relevance. There is no agreement as to which areas are the most important, there is no attempt to ensure claims are validated, there is no audit process for success/failure and no ranking of ability of individual units to complete projects and their value. This means that monies for research are often spent poorly.

Aim

1. Long-term aims

- To harmonise breast cancer research through individual funding organisations operating within Europe.
- To encourage research to be focused on that which will have ultimate clinical application.
- To ensure that validation is a part of the design of all applications.
- To establish an audit system backed by a database that allows assessment of the success rate of individual research groups.

2. Project-specific aims

- To bring together all organisations involved in developing, supporting and undertaking breast cancer research in Europe to design a strategy for the pan-European harmonisation of breast cancer research.
- To develop a process of audit of completed research whereby research projects will also be judged as to whether they have advanced the science and to what degree they are relevant to clinical practice.
- To maintain a database of projects and of the audit of completed projects.
- Audit of past projects and production of a policy paper for implementation.
- To influence journal editors, to ensure higher standards are set for acceptances for publication of results; validation and clinical relevance will be the most important issues.

Project number
LSSC-CT-2005-517659

EC contribution
€ 198 640

Duration
30 months

Starting date
01/01/2006

Instrument
SSA

Expected results

- A European overview process for project proposals received by all funding bodies. This will:
  - prevent research from being funded for similar work in multiple projects;
  - result in a few large, rather than multiple small data sets, which are much more likely to yield definitive results.
- Agreement and ranking of the areas most likely to give results of clinical relevance.
- Agreement on certain issues that must be included in all proposals (such as validation of the results).
- An audit process of the results of funded research. This will initially show if the contentions expressed above with regard to funded research are in fact correct. The audit outcomes will be accessible to research funders, in that institutes most likely to complete valuable projects will be identified (and the converse!).

Potential applications

Aside from the obvious and intended application in breast cancer funding across Europe, the model created by the project can be applied to many funding areas where multiple sources of funding create the same problems as seen in breast cancer.

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Keywords | Cancer pain | analgesic medicines | pain pharmacology |

NORMOLIFE

Development of new therapeutic substances and strategies for treatment of pain in patients with advanced stages of cancer

Summary

Prolonging the life expectation of patients with advanced cancer could be done by modern medicine. However, progressive pain that is associated with progression of the disease is the major factor that destructs the last moments of life. Severe progressive and uncontrolled pain is a major reason of requesting euthanasia. The applications of oral (morphine) pills or transdermal patches with lipophilic analgesic drugs are the most common treatments of cancer pain. These compounds penetrating into central nervous system produce side effects (respiratory depression, constipation, tolerance, sedation, etc.) to such extent that pain treatment is reduced by doctors or refused by the patients. The discoveries of the last years indicated the changes in expressions of pro- and antinociceptive receptors in pathologically changed peripheral tissues as well as in the central nervous system. The concerted modulation of these receptors in combination with designed receptor ligands may block nociceptive signal formation and transmission more effectively than traditional monotherapies. The objective of this project is to focus on the development of new multitarget compounds and methods which will interact with opioid receptors expressed in inflamed and/or pathologically modified tissues. Partial penetration into the central nervous system will result in synergistic pain suppression via interaction between the peripheral and central nervous system. Alternatively, newly developed compounds could be applied directly into central nervous system to interact with the specific, pathological set of receptors. The developed compounds will be screened *in vitro* in a cell silicon hybrid biosensor and selected compounds, *in vivo* in rodent's cancer pain models. The project will yield new basic data on structural requirements of analgesics for treatment of persistent cancer pain in advanced stages and will develop new compounds characterized to the stage that will allow to promote them for further clinical phase testing.

Problem

The approach in which compounds are designed to interact with a wide spectrum of targets involved in pain signal formation and transmission is a new and original therapeutic strategy, opposite to current strategies that use drugs which are as receptor-selective as possible. The project's major goal is chemical design of new multitarget molecules and analysis of their pharmacological properties that will result in the selection of several new compounds for further clinical evaluation as a new generation of potent analgesics for multicomponent cancer pain treatment.

Aim

The project will involve three general complementary scientific objectives: chemistry, *in vitro* biopharmacology and *in vivo* pharmacology that will be accomplished by multidisciplinary teams integrated in the project.

Synthesis of new compounds, designed by theoretical (SAR) analysis, will be synthesized in chemical laboratories. Hundred new compounds will be designed and synthesized on initial stages of the project. These compounds will be preselected in *in vitro* tests. The *in vitro* tests comprise receptor affinity evaluation and functional cell-based assays. The selected (expected 6) compounds will be finally characterized *in vivo* in an animal model of cancer pain.

Expected results

The application of a new generation of medicines designed under the NORMOLIFE project will reduce side effects generated by traditional opioids in central nervous system, including tolerance, dependence, constipation, euphoria, etc. The major prospective application of the results will be a more effective treatment of acute as well as chronic, neuropathic and inflammatory cancer pain of patients with advanced stages of the disease. We predict that the project will be able also to define the differences between the spectrum of pain symptoms and pain progression in progressive cancer typical for female (ovarian) and male (prostate) patients. The establishment of such differences will help to propose different pain treatment for women and men.

Potential applications

The experimental preclinical data of the newly-developed compounds will allow for selection and proposition of new medicines for further clinical evaluation.

Nerve cells cultured on a micro-electrode chip for testing analgetics. (Foto C. and M. Kage)

Project number
LSHC-CT-2006-037733

EC contribution
€ 2 182 325

Duration
36 months

Starting date
01/12/2006

Instrument
STREP

Project website
www.normolife.eu

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Scientific Model Systems

The complexity of cancer initiation and progression combined with heterogeneity of different cancers presents a big challenge to researchers studying this disease. In order to overcome these difficulties cancer research often has to rely on model systems that can be used as examples of other systems that are more difficult to study directly. Good model systems have to be sufficiently simple to be studied, but at the same time sufficiently complex to allow for generalisation of the study results. The model systems have to mimic the problem under investigation and to be reproducible. Advantages of their use in cancer research include time and cost efficiency and relative ease to control for the factors involved. Development and characterization of new model systems – be it living organisms or computer software capable of reproducing some processes involved in cancer biology or investigating potential treatments – and technologies that facilitate their use is of the utmost importance in current cancer research.
This area of research is represented by two projects that answer to the need for better cancer models in very different ways. ESBIC-D is a Coordination Action that aims to establish a framework for a systems biology approach to combat cancer by creating a network of partners with different expertise on the European level. ZF-Tools is a STREP project aiming to develop and characterize a zebrafish model system that could be used as a high-throughput screening tool in drug discovery research.

Dominika Trzaska

Keywords | Systems biology | computational biology | cancer research | modelling | signalling pathways | bioinformatics and patient information |

ESBIC-D

European Systems Biology Initiative combating complex diseases

Summary

It is the goal of this coordination action (CA) to establish a European framework for a systems biology approach to combat complex diseases using cancer as a prototypical problem. The coordination action will be fundamentally based on existing resources of leading research groups in Europe. It unites groups with a strong clinical focus, with experience in high throughput functional genomics as well as with computational and systems biology resources. Moreover, it brings together groups from some of the largest European cancer research organisations and centres.

Problem

Primary targets of the Sixth Framework programme are activities for the combat of multigenic complex diseases such as cancer, diabetes, obesity, heart diseases and diseases of the nervous system. In particular, cancer is, after decades of research, still a devastating disease, responsible for roughly one quarter of the death in Europe.

Essentially, the three main causes for cancer are infection, environmental influence and genetic predisposition. However, on a more analytical and molecular level the ontogeny of cancer is less evident and both clinical as well as basic research suggests that cancer is the result of an accumulation of many factors that promote tumour growth and metastasis. Consequently, it is not clear, if much of current cancer research, typically focussed on analysing subprocesses involving at most a few genes or gene products at a time, will ever be able to 'understand' such a complex phenomenon, and to form the basis for dramatic improvements in cancer treatment. It is also clear, that the current research approaches, in spite of all successes in some areas, have not resulted in any dramatic increase in the rates of cure for most common cancers.

With this CA we expect to improve this situation by addressing the problem with a systems biology approach. In particular, the strong interaction of clinical and experimental data with theoretical computer modelling will be applied in an interdisciplinary and international approach.

This goal will be achieved via a series of steps:

- designing the protocols needed for rapid data and information exchange for the different levels of cellular information;
- connecting leading European research groups in a consortium that contributes existing data and computational resources and links clinical and experimental groups with computational groups;
- providing standards and protocols to combine the data resources with theoretical models;
- providing documentation and a series of workshops to achieve the largest possible benefit for European cancer research.

These interaction points between the different expertises build the basis for measurable and verifiable targets of the project that will have a high impact on future planning and design of systems biology approaches for all complex genetic diseases.

Aim

Exchange and dissemination of information – combining leading EU wide resources. A particular goal of this CA will be the agglomeration and integration of relevant information from all three components. Existing resources of the partners/partner institutions will be incorporated and an immediate added-value is achieved on the European level by the correlation and integration of those components.

Performance of joined studies and analyses – bridging experiment and model. There is a fundamental discrepancy in current cancer research. Much of the analysis carried out up to now has been focussed on the effect of single genes, resulting in models that are far too simple to explain the complex biological processes acting in cancer development. Thus, modelling at the state of the art is in most cases not very helpful for e.g. prediction of the response of patients to different types of treatment or the development of new drugs. On the other hand there is the tendency to generate more and more data in an uncoordinated and non-standardized fashion. This not only increases costs but also leads to heterogeneous and often conflicting results for the relevant biological processes. Thus, experimental data generation at the state of the art is not very helpful to guide the development of theoretical models. With this CA we aim at identifying critical parameters in the course of such model development and the identification of experimental protocols and strategies to measure these critical parameters in coordinated experiments that target different levels of cellular information.

Project number
LSHG-CT-2005-518192

EC contribution
€ 350 000

Duration
24 months

Starting date
01/11/2005

Instrument
CA

Project website
http://pybios.molgen.mpg.de/ESBIC-D

Performance of benchmarking exercises – defining test cases for systems biology approaches in cancer. There are many promises for health care: models of regulatory networks are necessary to understand their alterations in case of a disease and to develop methods to cure the disease. Furthermore, since there is an observable trend in health care towards an individualized and predictive medicine there will be an increasing need for the exact formulation of cellular networks and the prediction of systems behaviour in the areas of drug development, drug validation, diagnostics, and therapy monitoring. In this project we will define several test cases that will show for example the performance of models for signalling pathways in the light of the experimental data resources.

Organisation and management – setting up an expert group for a European wide systems approach towards the combat of cancer. So far, on the European level, there are some excellent groups and networks that focused their work in particular fields of genomics, proteomics, clinical research and bioinformatics. While on the one hand theses areas will need additional strengthening to remain competitive on an international level, we are still lacking an initiative that brings together these groups to find common and efficient ways to integrate and to utilise the data produced. This will be a first necessary step to create a European platform for systems biology of complex diseases/cancer. Consequently a coherent structure for data acquisition and data integration for modelling has to be built. For this purpose we need to:

- define cancer related clinical, genomic and proteomic data sets in the context of systems biology;
- improve ways of data acquisition, storage and communication procedures;
- set standards for quality data integration;
- define common targets of systems biology modelling in cancer.

Expected results

A coordinated action for the systems biology of cancer will create an expandable network of partners that develop efficient tools for data collection, integration and modelling. In the future, this will improve our understanding and in particular our prognostic and therapeutic abilities for the complex genetic disease cancer.

Potential applications

Not applicable.

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Keywords | Zebrafish embryo model | functional genomics | tumor markers | defence response | cell transplantation |

ZF-TOOLS

High-throughput Tools for Biomedical Screens in Zebrafish

Summary

The zebrafish embryo model has rapidly gained ground in biomedical research based on functional genomics approaches. As a result it shows great potential to be incorporated into preclinical drug screening pipelines. ZF-TOOLS aims to develop a case study for an anti-tumor drug screening system, based on implantation of fluorescently labeled tumor cells into zebrafish embryos. The optically transparent embryos provide a highly useful *in vivo* system to monitor growth and metastasis of implanted tumor cells. This system will allow for the powerful combination of visual monitoring with high-throughput analysis of expression of marker genes with a predictive value for tumor progression or for defence responses towards developing tumors. However, the bottleneck for application of this approach is insufficient knowledge of relevant disease marker genes in zebrafish. Therefore, the first objective of ZF-TOOLS is marker discovery. To achieve this objective fluorescent zebrafish cell lines expressing selected oncogenes will be generated and a multidisciplinary functional genomics approach, integrating different genomics techniques and bioinformatics, will be undertaken to compare expression profiles before and after implantation into zebrafish embryos. The experimental design of our genomics strategy will enable distinction between tumor cell markers and markers for immune or general defence responses of the organism. After marker validation, high-throughput tools for large scale expression screens will be developed. The second objective of ZF-TOOLS is to exploit the combination of high-throughput markers and implant system to study different oncogenic implants and effects of a test panel of drugs used in human cancer therapy. This case study should result in identification of important tumor growth and metastasis factors as well as defence factors. Fundamental knowledge, tools and technical expertise gained from ZF-TOOLS will be commercially exploited by three high-tech SMEs.

Problem

The ZF-TOOLS objectives are focussed on the incorporation of the zebrafish embryo model into the preclinical drug screening pipelines. The use of mice for *in vivo* monitoring of disease processes such as tumorigenesis, metastasis and immune response to tumors is limited by costs and throughput level. Introducing a high-throughput zebrafish embryo model could potentially contribute to cost-effective and more efficient methods in the anti-tumor drug discovery process. Acceleration of drug lead time benefits economy as well as quality of life of cancer patients.

The lack of basic knowledge of disease marker genes is the current bottleneck for biomedical research in zebrafish and for genomics-based compound screens in this model organism. The ZF-TOOLS project uses multidisciplinary functional genomics approaches to discover novel disease markers. The expected identification of factors important for tumor growth and metastasis and organismal defence responses will contribute fundamental knowledge relevant to human health and will open the door to the establishment of zebrafish-based biomedical research and screening tools.

Aim

The ZF-TOOLS project is a coordinated effort of three research laboratories and three SMEs aimed at the following objectives:

- genomic-based marker discovery for biomedical screens in zebrafish;
- use of high-throughput marker analysis and tumor cell implants for the identification of tumor growth and metastasis factors and organismal defence factors.

The project aims to develop a case study for an anti-tumor drug screening system, based on the implantation of fluorescently labeled tumor cells into zebrafish embryos. This innovative tumor cell implantation system is currently being developed by one of the SME partners in the project and has the major advantage that it does not involve the use of transgenic animals. Growth and metastasis properties of implanted tumor cells can be efficiently monitored by fluorescence microscopy during development of the transparent zebrafish embryos. The system resembles the natural situation of tumor growth, as the tumor cells are derived from zebrafish cell cultures of embryonic origin and implanted back into zebrafish embryos. We envisage that a powerful screening system can arise from the combination of high-throughput marker analysis with the possibility to visualize tumor growth and metastasis in an optically transparent vertebrate model organism. However, for realization of such a screening system, the identification of relevant disease marker genes in zebrafish forms a crucial step. In the ZF-TOOLS project different genomics approaches will be used to discover novel markers, which will be suitable for application in the ZF-TOOLS tumor screening system and also will have a broader utility for disease research in the zebrafish model.

The experimental design of our genomics approach is expected to result in the identification of two classes of markers:

- markers correlating with growth and metastasis of tumor cells;

Two-day-old zebrafish embryo.

- markers correlating with the immune or other defence responses of the organism towards tumor cells.

The reason for concentrating on both classes of markers is that interactions between developing tumors and the tumor microenvironment are decisive for tumor survival or rejection. Strategies to boost anti-tumor immunity have been explored for many years. Therefore, knowledge of tumor markers as well as defence response markers will increase the versatility of the anti-tumor drug screening system to be developed in the project.

Based on the genomic analyses in the project, tools will be developed for high-throughput simultaneous quantification of defined subsets of relevant marker genes. Next, the combination of high-throughput marker analysis and the tumor cell implantation system will be applied to investigate different oncogenic cell implants and to carry out a case study with a test panel of drugs used in human cancer therapy. This will allow assessment of which markers represent important factors with roles in tumor growth and/or metastasis or roles in defence responses. Knowledge of these factors is expected to form a solid basis for further development of a powerful screening system that can be offered to the pharmaceutical industry after the project. Furthermore, technical expertise in development and application of high-throughput analysis tools will be used to expand the service activities of SMEs involved in the project and strengthen their position. Finally, basic knowledge of disease markers, an expected achievement of the project, is indispensable to advance biomedical research in the zebrafish model.

Expected results

The strategic aim of the ZF-TOOLS project is the development of a zebrafish embryo screening system as an innovative genomics tool. This system will be employed for high-throughput effectiveness testing of pharmaceutical compounds that have the potential to influence disease processes including tumor growth, metastasis and immune defence responses. This zebrafish screening tool offers some unique features that make it very attractive in comparison with existing tools:

- it combines the power of genomic analysis of disease marker genes with the power of in-vivo monitoring of disease processes in a transparent vertebrate model organism;
- it has the potential for high-throughput application due to the small size of zebrafish embryos, the high numbers with which embryos can be obtained and the choice of high-throughput molecular screening tools that will be developed within the project.

In order to establish the zebrafish screening tools, the ZF-TOOLS project will undertake a multidisciplinary functional genomics approach integrating different global expression profiling techniques and bioinformatics. High-throughput tests for expression screening of defined sets of newly identified disease marker genes and disease-associated small regulatory RNAs will be developed. In addition, based on genomic data resulting from the project, a collection of novel oncogenic and fluorescent reporter cell lines will be developed, suitable for implantation into zebrafish embryos and in-vivo monitoring of tumor growth and metastasis processes. These cell lines also offer the attractive possibility to perform complementary, *in vitro* cell culture based screens. With this approach the ZF-TOOLS project is expected to result in:

- knowledge of tumor growth and metastasis factors and organismal defence factors;
- high-throughput tools for quantitative analysis of disease marker sets;
- a collection of constitutive and inducible, oncogenic and non-oncogenic reporter cell lines useful for basic disease research and for application in screening systems;
- case study results of a novel anti-tumor drug screening system, based on the implantation of fluorescently labeled tumor cells into zebrafish embryos.

Potential applications

The ZF-TOOLS project aims to make an impact on reinforcing European competitiveness by generating strategic knowledge in a multidisciplinary research approach. The studies to be carried out within the ZF-TOOLS project will result in the development of novel tools for biomedical research and pharmaceutical screenings as well as in technical expertise that will be valuable to a broad range of research topics. These tools and technology will be exploited for basic research of vertebrate disease as well as for strategic research and service activities of three high-tech SMEs.

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