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VACCINES FOR HUMANS

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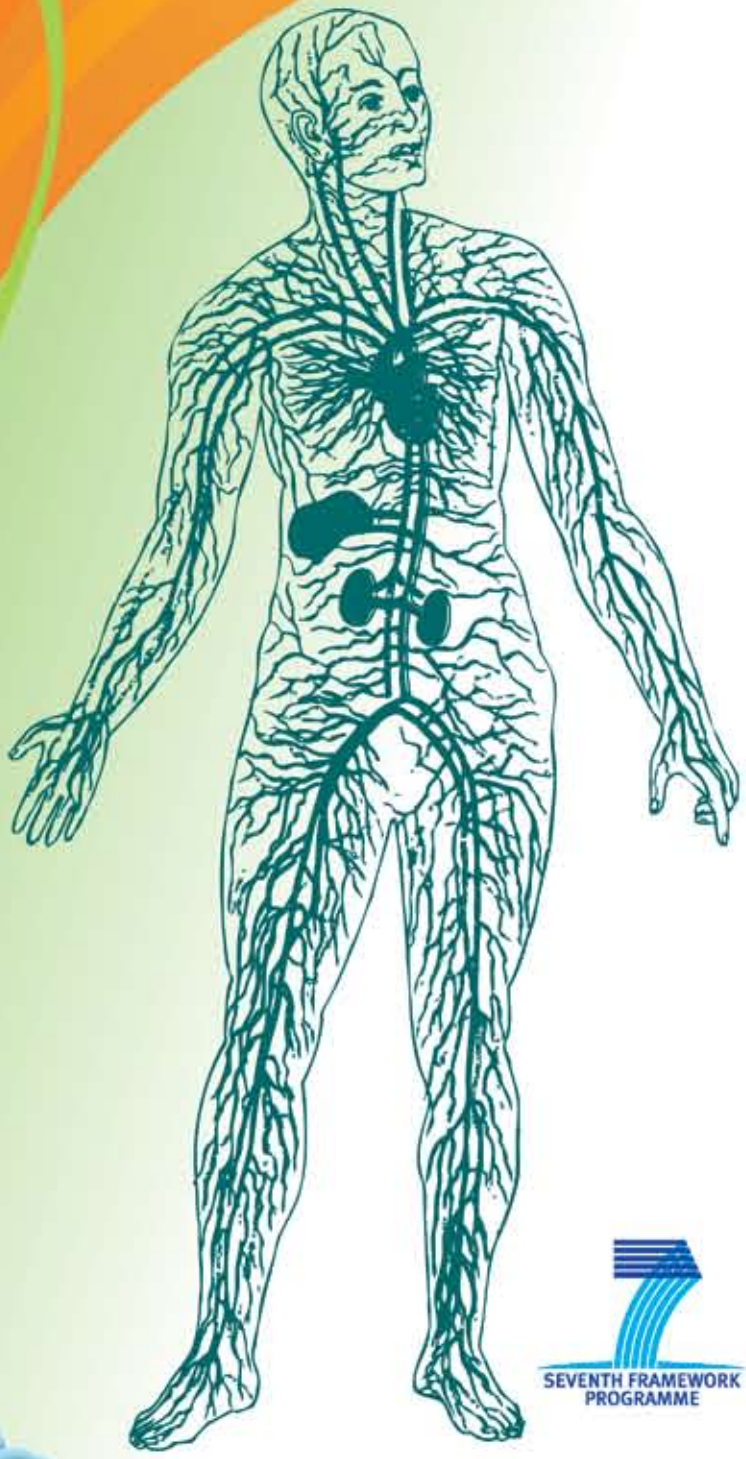

SEVENTH FRAMEWORK PROGRAMME

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EUROPEAN COMMISSION

VACCINES FOR HUMANS

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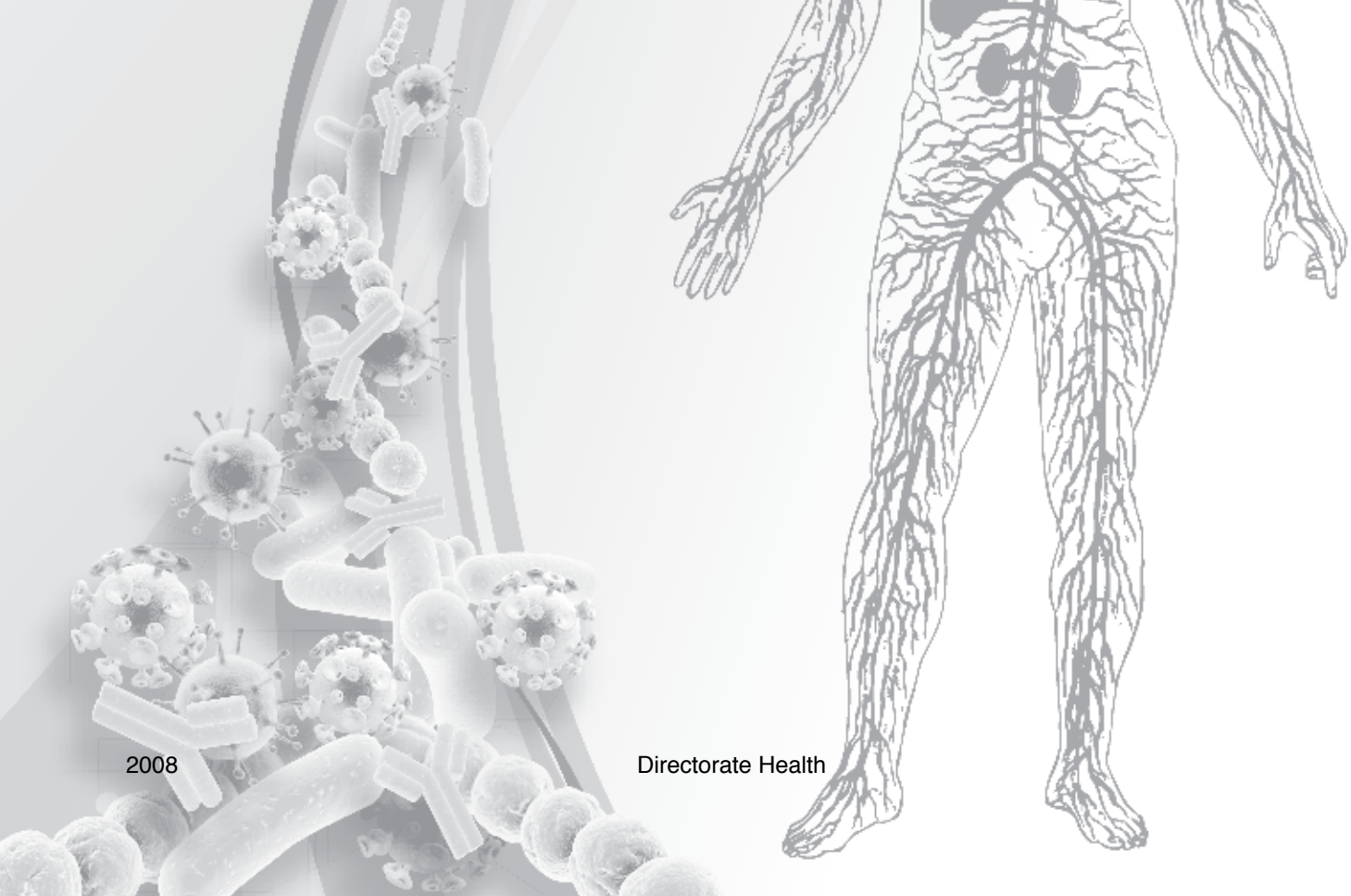

2008

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Luxembourg: Office for Official Publications of the European Communities, 2008

ISBN 978-92-79-09455-2
DOI 10.2777/84341

Printed in Belgium

PRINTED ON WHITE CHLORINE-FREE PAPER

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HUMAN VACCINE RESEARCH IN THE EUROPEAN UNION

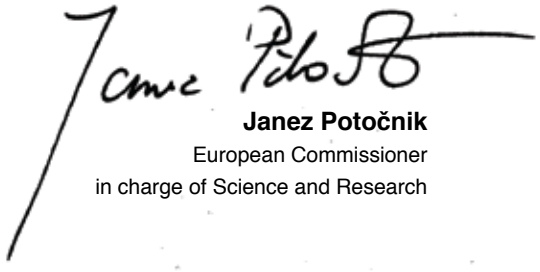
The use of vaccines is saving millions of lives every year, and the tale of vaccines is one of the greatest success stories in medical history. Vaccines were responsible for the eradication of smallpox in 1970, the eminent eradication of polio and possibly the future eradication of measles. Vaccines can be thanked for millions of lives saved every year from diseases such as tetanus, hepatitis, and flu, but also for economic stability and development in countries where diseases such as mumps, rubella and diphtheria were previously responsible for millions of working hours lost to sickness, disability and care of relatives.

The great success of vaccines in the past and present should be used as inspiration to intensify research in this area of life science even further. A number of important infectious diseases such as HIV/AIDS, malaria and hepatitis C are thus continuing to escape attempts to produce effective vaccines against them. Vaccines against a number of other infectious diseases such as TB and influenza exist, but are only partially effective and need dramatic improvement to respond to the real public health needs. Furthermore, the emerging possibility of preventing, treating or halting a range of non-infectious diseases through vaccine approaches is one of the most exciting frontiers in medical science, and it holds huge potential to cover unmet medical needs in areas such as cancer, autoimmune diseases and neurology.

Europe has a long and successful tradition of vaccine research in both public and private institutions. Europe is also home to many of the world's oldest and largest vaccine manufacturers. Europe is therefore well positioned to take on new challenges in vaccine research, and exploit the immense opportunities that are opening up in this field of science. The Sixth Framework Programme (FP6), which was adopted by the European Commission (EC) in 2002, was an important catalyst in this direction and allocated substantial support to European vaccine research. FP6 made it possible for the first time for the EC to support large-scale multidisciplinary consortia with a focus on translational research, while also supporting smaller projects to explore highly innovative ideas and concepts.

The vast majority of vaccine and vaccinology activities in FP6 was funded through the Health theme, although important contributions came from the Food theme, the Information Society theme (IST) and from cross-cutting activities on international cooperation (INCO), and the support activities to small and medium-sized enterprises (COOP). Furthermore, vaccines for zoonotic diseases were predominantly supported through the Food theme.

This publication compiles the projects on human vaccines and vaccinology that have been supported through the Sixth Framework Programme. By doing so, it provides evidence of a vibrant, visionary and ambitious community of European vaccine researchers. It also shows how hundreds of scientists are working across Europe to discover and develop new vaccines for the world. It goes without saying that the European Commission will seek to maintain Europe's leading position in this important area of research by providing continued support to vaccine research throughout the Seventh Framework Programme (2007-2013).



Janez Potočnik
European Commissioner
in charge of Science and Research

INTRODUCTION

EUROPEAN VACCINE RESEARCH

Vaccine research has seen a remarkable renaissance during the last decade. This has partly been catalysed by scientific breakthroughs such as the full genome sequences of several infectious pathogens, and refined knowledge about the immune system and its response mechanisms. The other major factor has been a significant influx of money from public funding bodies, private charity organisations and commercial enterprises. In the private sector, recent commercial successes such as the human papilloma virus (HPV) vaccine have triggered small and even large pharmaceutical companies to initiate or renew their interest in vaccines. This trend has been further supported by the appearance of novel financing mechanisms such as Product Development Partnerships (PDPs), and the introduction of market-related incentives such as the Vaccine Fund, the Advanced Market Commitment (AMC) and the International Financing Facility for vaccines.

There are several reasons for the European public sector to engage actively in vaccine research and to support the development of new effective vaccines. Firstly, vaccines are one of the most effective ways to protect people against infectious diseases and thereby actively promote better health and quality of life, locally as well as globally. Secondly, vaccines are one of the most cost-effective measures for public health. Safe and effective prophylactic vaccines are significantly more cost effective than repeated applications of drugs and other treatments. Vaccines can thereby release health sector cash, which can instead be used elsewhere in the health system. Thirdly, the development of vaccines against extraordinary pathogens such as HIV may be so technically and scientifically challenging that it may never occur without sustained support and active contribution from the public sector. Addressing very challenging pathogens may, on the other hand, lead to scientific breakthroughs with a broader application to technological and economic development. Last but not least, vaccines against pathogens such as dengue or malaria, that are mainly (or only) prevalent in low-income countries, are unlikely to be developed unless the public sector subsidises and supports research. In this respect, international public organisations such as the European Commission have a particularly important role to play as they can act with a higher emphasis on the global health agenda rather than national research priorities.

During the course of FP6, the European Commission has supported a wide variety of vaccine research activities with relevance for human health. Taken together, more than EUR 410 million was allocated to research projects with focus on vaccines or projects with relevance to vaccines or vaccinology aspects. Broadly speaking, three different types of vaccine research have been funded (Fig 1): new, innovative approaches to vaccinology and vaccine development have been funded with a view to develop and mature highly innovative technologies and vaccinology concepts. In this area of activity, the EC has funded 15 projects with more than EUR 46 million in total. Most projects, namely 42, were funded in disease specific vaccine research. This resulted in a total EC contribution of EUR 136 million. In budgetary terms, the largest supported area was clinical vaccine research and capacity building, which received a total of EUR 230 million. It should be noted that this figure includes an EC contribution of EUR 200 million to the European and

	Basic Vaccinology	Disease specific vaccine research	Clinical Research and capacity building	**TOTAL**
Number of projects	15	42	10	**67**
Total EC contribution (million euros)	47	134	229	**410**

Fig. 1: Overview of EC funded human vaccine research in FP6

Developing Countries Clinical Trials Partnership (EDCTP) initiative. The EDCTP initiative is an independent legal entity that supports capacity building and clinical trials of new vaccines and treatments for HIV/AIDS, malaria and TB in sub-Saharan Africa. Only a part of the total EDCTP activities are therefore dedicated to vaccine research and vaccine related activities, albeit an important and crucial part. Other activities supported in the area of clinical research have focused on increasing the knowledge and efficacy of existing vaccines.

Different magnitudes of projects have been supported within each category. Large Integrated Projects (IP) have been used to support multi-disciplinary consortia with sufficient critical mass to translate basic research results into applications. Smaller and focused research activities have been supported using Specific Targeted Research Projects (STREP). This instrument has typically been used to develop innovative concepts or discovery of new vaccine candidates. Networks of Excellence (NoE) and coordination actions (CA) have been used to structure and organise the European research community around common research agendas. Strategic Support Actions (SSA) have been used to support small, targeted supporting activities such as conferences, workshops or training activities.

The vast number of projects were STREPs, which constitute more than two thirds of all projects (Fig. 2). However, it is the IPs that form the core of the EC funding pipeline. Due to their large size and critical mass of multidisciplinary participants, the IPs may act as uptake of new discoveries from smaller, innovative projects, while delivering matured project results in the other end for clinical applications or further downstream development by industry organisations, the EDCTP, or public-private partnerships.

The EC believes that tighter collaboration between multiple stakeholders is central to the advancement of health science. A key component of the EC Framework programme is therefore to promote cooperation between researchers in different countries, and across sectors and disciplines. While undertaking major research activities, these partnerships are also contributing to a long-term restructuring of the European research community.

During FP6, a total of 575 research groups participated in human vaccine research projects (Fig. 3). The vast majority was located in EU Member States (84%), but increasing globalisation in health science means that more and more participants come from other countries, either European non Member States (7%) or non European countries (9%).

	EDCTP	IP	STREP	NoE	SSA
Number of projects	1	10	46	3	7
Number of participants	16	163	319	79	27
Total EC contribution (million euros)	200	103	80	24.5	2.8

Fig. 2: Overview of instruments used for funding vaccine research in FP6

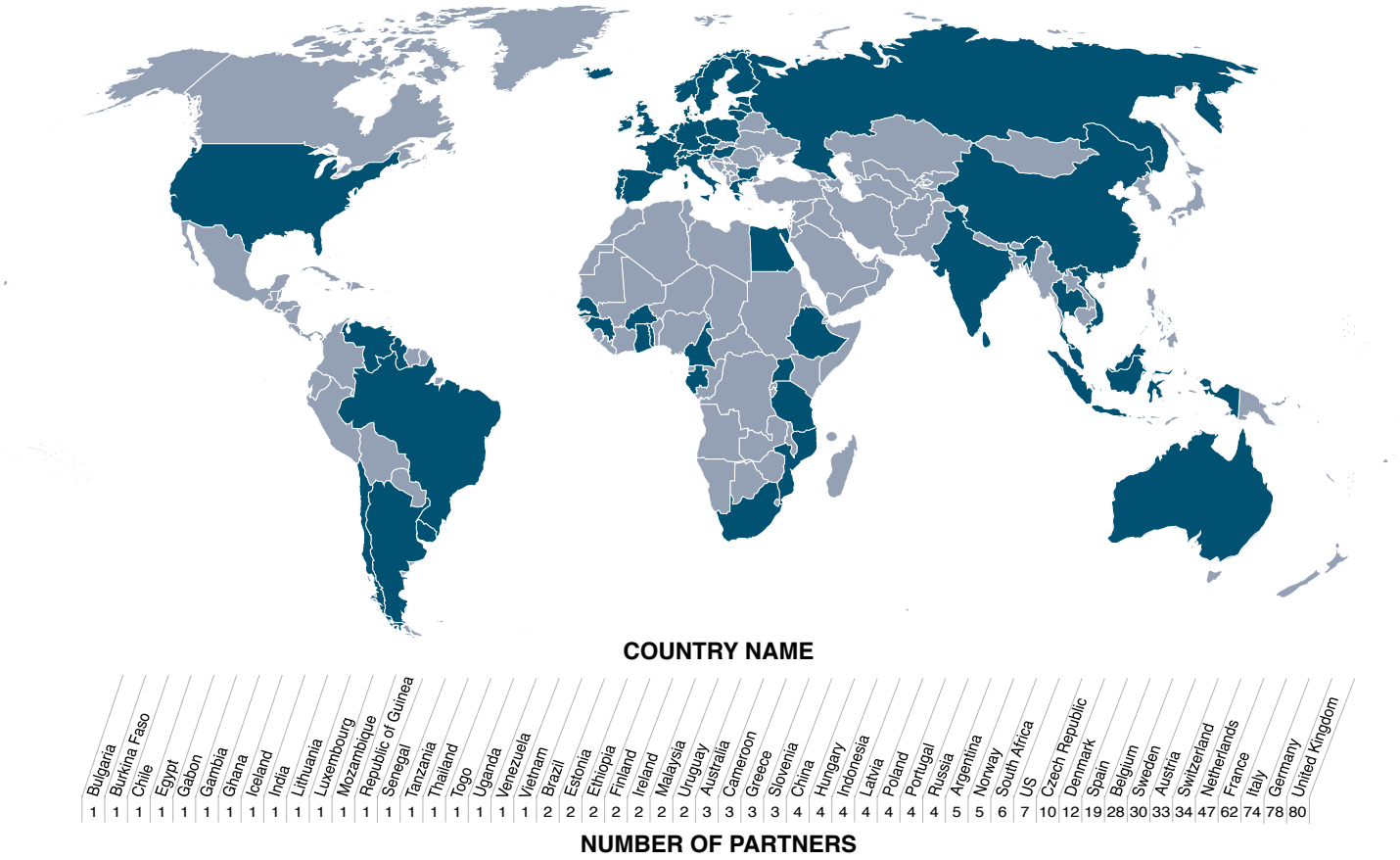


Fig. 3: Participants in EC funded human vaccine research in FP6 come from a large number of different countries.

Significant efforts were also made to build partnerships between scientists in different sectors. The result has been that more industry partners have participated in vaccine research projects in FP6 than in any previous framework programme. The industry partners include small and medium-sized enterprises (SMEs) as well as large and established vaccine companies. In total, more than 10% of all partners in the EC funded vaccine projects came from the private industry sector.

At the beginning of 2007, FP6 was followed up by the introduction of the Seventh Framework Programme (FP7), in which Health research plays an equally important role as in FP6, and with an even higher average annual budget. FP7 runs from 2007 to 2013, and has a budget allocation of EUR 6 billion to cooperative Health research, corresponding to an annual average of approximately EUR 900 million. The objective of this programme is to support a wide range of top-quality research activities in transnational cooperation across Europe and increasingly globally.

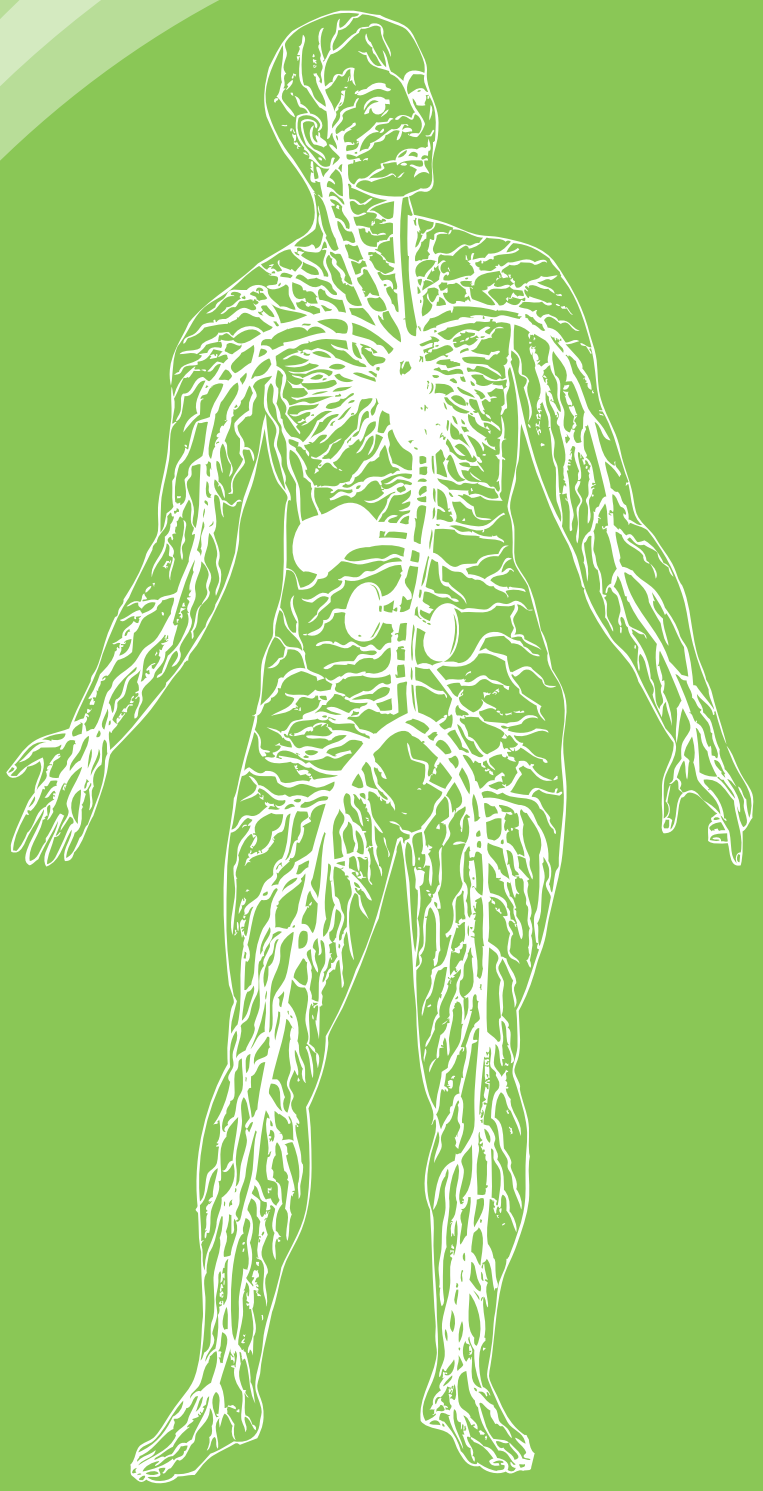
Activities in poverty-related diseases (HIV/AIDS, malaria, TB) remain a key activity in FP7, but the area of infectious diseases has been strengthened by including two new dedicated activity areas for Emerging Infectious Epidemics and Neglected Infectious Diseases. Emerging Infectious Epidemics will fund research on upcoming threats from emerging viral infections to European health, while activities in Neglected Infectious Diseases will address a range of protozoan, bacterial and helminth infections of significant importance to global health in resource poor countries. FP7 will continue to support research in basic vaccinology in both infectious and non-infectious diseases, primarily through pillar I of the Health programme, which is dedicated to “Biotechnology, Generic Tools and Medical Technologies for Human Health”. Last but not least, FP7 will also provide continued support to research in a range of non-infectious diseases, for example cancer, neurodegeneration and autoimmune diseases, where vaccine approaches are becoming increasingly relevant.

The European vaccine research in FP6 is pointing towards the creation of a new, promising patchwork of collaboration within the vaccine research community across Europe and beyond. The focus on translational research in the health theme of FP7 makes it feasible to accelerate European vaccine research even further, and translate the most promising results into application. FP7 is thus well equipped to provide sustained support to the wide range of successful vaccine research that was initiated in FP6.

OLE F. OLESEN

Acknowledgements: This publication was compiled by Ole F. Olesen and Rachida Ghalouci with the assistance of colleagues in DG RTD of the European Commission, and with the invaluable help of friends and collaborators in the European vaccine research community. Special thanks go to Alain Vanvossel (Head of Infectious Diseases), Anna Lonnroth (Deputy Head of Infectious Diseases) and Bernard Mulligan (Deputy Head of Genomics and Systems Biology) for sustained support to compile this catalogue. Similarly, our thanks go to Virginie Braconnier and Evelyne Bastin for secretarial assistance, and to Yiannos Contrafouris for technical and editorial support.

BASIC VACCINOLOGY



INTRODUCTION

BASIC VACCINOLOGY

Vaccine research has come a long way in the past 20 years, with technological break-throughs that are paving the way for innovative and more efficacious vaccines against a host of pathogens and pathologies. The application of modern biological technologies and advances in our understanding of genomic knowledge has resulted in new concepts like reverse vaccinology, DNA vaccines, recombinant subunit vaccines and non-replicating vectors. Many of these new concepts are now being applied around the world to specific diseases and pathogens, and some have already progressed to advanced clinical trials and new products such as the meningococcal vaccine and hepatitis B vaccine. Recent years have also seen significant advances in our understanding of the control mechanisms of the immune system, as well as the mechanisms underlying both acquired and innate immunity. Yet, a further understanding of basic mechanisms in the immune system is needed to fully exploit the immense possibilities of modern vaccinology.

Many researchers are contributing to this exploration of the human immune response, which eventually could enable the development of future vaccines against some of the most challenging pathogens and diseases. The EC has participated in the global efforts to a better understanding of basic vaccinology by allocating almost EUR 50 million to research in this area. The funding has been shared between 15 research consortia, all of which are focused on knowledge and technologies with broader relevance for vaccine development.

The 15 EC funded projects have addressed a wide variety of important aspects in basic vaccinology (Table 1), although 3 activity areas have received particular attention, namely mucosal vaccinology; post-genomic vaccinology and dendritic cells as vaccine targets.

Research Area	Project Acronym	EC Contribution	Number of Partners
Topical vaccinology	MUVAPRED	15.250.000	29
	EPIVAC	2.400.000	7
	MuNanoVac	1.505.702	8
Genomic Vaccinology	CompuVac	7.969.442	15
	BacAbs	2.269.999	9
	MICROBEARRAY	1.401.002	9
Dendritic cells	DEC VAC	3.400.000	10
	DC-VACC	2.000.000	9
	THERAVAC	2.267.000	7
Explorative vaccinology	AIDS-CoVAC	958.000	3
	HIVAB	950.000	7
	INNOVAC	2.000.000	7
	ImmunoGrid	1.950.000	8
	VaccTIP	1.000.000	5
	MVACTOR	1.000.000	4

Table 1: EC-funded projects in basic vaccinology

Many infectious diseases are caused by pathogens that enter the human body through mucosal surfaces. This includes such prominent diseases as HIV/AIDS, TB, influenza and sexually transmitted diseases. Many of these diseases could be better confronted if the causing pathogen could be stopped at the first port of entry to the human body. This requires a detailed understanding of the delicate interplay between antigens and adjuvants during mucosal immunisation as well as an understanding of the relationship between the systemic and mucosal immune system. Two EC funded projects are addressing this, namely the MUVAPRED integrated project, which explores how an effective and lasting immune response can be induced at mucosal surfaces, and the MuNanoVac STREP project, which explores the possibility of using nanoparticles as a vehicle for mucosal immunisation. A related project, EPI-VAC, addresses local immunology, and is focused on transdermal immunisation with DNA vaccines. Taken together, more than EUR 19 million has been allocated to research activities on mucosal and/or local immunology. This corresponds to 40% of the total EC contribution to basic vaccinology, and confirms the importance of this area within the EC portfolio of vaccine research activities.

Another key area of research has been the use of new genomic data for better selection of new vaccine candidates. This is the core activity of the Compuvac project, which gathers 15 partners in a joint effort to develop a platform for Rational Design and Standardised Evaluation of Genetic Vaccines. BACABS is a STREP project which focuses on establishing a standard approach for selection of vaccine candidates, mainly on the basis of structural determinants. Together with Microbearray, another project in this category, these projects have received a total EC funding of more than EUR 11 million, corresponding to approximately 25% of the funding to basic vaccinology.

The third major area of funding for basic vaccinology is the potential utilization of dendritic cells for various vaccine approaches against both infectious and non-communicable diseases, including cancer. This is an exciting, but also challenging area of vaccinology. The ability to induce a controlled immune response against endogenous proteins that are present in abnormal amounts or conformations could be the key to the development of prophylactic or therapeutic vaccines for a wide range of diseases such as AIDS, cancer, autoimmune diseases and degenerative diseases. Most of the current vaccines work by inducing an antibody response, but using vaccines against many types of diseases, infectious as well as non-infectious, may require a concurrent induction of a cytotoxic T-cell response. To achieve this, a better understanding of the role of dendritic cells in the immune system is necessary. The project DEC-VAC aims to enhance antigen uptake, and presentation by dendritic cells (DCs) of either protein vaccines, peptide vaccines, DNA vaccines or viral vector vaccines, thus providing a broad vaccination platform. The two STREP projects DC-VACC and Thera-vac explore the potential future use of dendritic cells as natural adjuvants and targets for a broad range of vaccines.

Other areas of basic vaccinology have been supported by the EC through a number of STREP projects. These projects have explored a wide variety of vaccine research, ranging from the use of new vectors for vaccine development (MVACTOR), the development of new vaccine strategies for both innate and adaptive immune responses (VaccTip) to the establishment of a virtual immune system (Immunogrid).

The projects on basic vaccinology are thus covering a wide range of activities. They are opening new avenues for vaccine development, and by establishing new methods and introducing novel technologies they are creating the “toolbox” of future vaccine research. Albeit that many of the projects are highly risky, they are also associated with a high potential impact on vaccine development that may be applied across a range of diseases.

MUVAPRED

MUCOSAL VACCINES FOR POVERTY-RELATED DISEASES

Acronym:	MUVAPRED
Project number:	LSHP-CT-2003-503240
EC contribution:	€ 15 250 000
Duration:	60 months
Type:	IP
Starting date:	1 December 2003
Project website:	www.mucosalimmunity.org/muvapred

BACKGROUND

HIV/AIDS and TB have caused an unprecedented global health crisis, accounting for more than 4 million deaths each year, with the majority of these in developing countries, particularly sub-Saharan Africa. Since the start of the HIV epidemic, 21 million people have died and 57 million people have become infected. *Mycobacterium tuberculosis* affects one third of the world's population and represents the main cause of death in HIV-infected patients. Furthermore, TB represents a dramatic problem in eastern Europe because it is highly drug-resistant. This epidemiological situation is a major problem for all of Europe, due to the impact of the spread of clinically relevant strains (World Health Organization report, 2002).

No vaccines have been developed for HIV yet, and the efficacy of the BCG vaccine currently being used in different populations and regions ranges from 0% to 80%. Despite this, vaccination is one of the most cost-effective interventions; the economic value associated with vaccines (mainly those for developing countries) is negligible.

Most existing vaccines are still administered by systemic injection. Although widely accepted, parenteral vaccination has potential drawbacks. Most of the pathogens invade their human hosts at the level of the mucosal surfaces, which represent the very first antimicrobial barrier through non-specific (anatomical) and specific (immune) defence mechanisms. Mucosal vaccination would offer several advantages over the parenteral route of vaccination. Inducing local microbial-specific immune responses would block pathogens at the port of entry, thus increasing the general efficacy of the vaccine. By avoiding the traumatic procedure of injection, mucosal vaccination would increase compliance and consequently coverage. It would also facilitate vaccine delivery, especially in poorer countries, and would significantly decrease the risk of infectious agents spreading via contaminated syringes.

AIMS

Human Immunodeficiency Virus and *Mycobacterium tuberculosis* enter the human body at mucosal sites. This Integrated Project aims to develop mucosally delivered vaccines against HIV and TB, which will induce local immunity able to neutralise the pathogens at their port of entry, and systemic immunity able to prevent the systemic spread of the infection. The possible development of mucosal vaccines against malaria is also being investigated.

In the project existing antigens, which are known to be protective in animal models against HIV and TB, are being formulated for mucosal delivery and tested in clinical trials. The antigens used for the initial clinical trials are the latest generation of the envelope protein of HIV, which, being deleted from loop 2, unmasks some of the conserved epitopes and induces broadly neutralising antibodies against primary isolates of HIV and the fusion protein of Ag85B and ESAT-6 of TB.

While the first trials are being performed, new systems to deliver mucosal vaccines and basic mechanisms of mucosal immune responses and memory in humans are being studied. This will allow a better understanding of the clinical results, and optimisation of second-generation vaccines to be tested in developing countries. The project's intention is to provide candidate mucosal vaccines against HIV and TB that could subsequently enter the path towards licensure through phase II and III clinical trials in developing countries.

EXPECTED AND OBTAINED RESULTS

MUVAPRED has targeted the clinical demonstration of safety and immunogenicity in healthy volunteers of vaccine candidates against HIV and TB infections. The results will advance safe and powerful mucosal vaccines in efficacy trials in developing countries.

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EPIVAC

DEVELOPMENT OF A MULTI-STEP IMPROVED EPIDERMIS SPECIFIC VACCINE CANDIDATE AGAINST HIV/AIDS

Acronym:	EPIVAC
Project number:	LSHP-CT-2006-037651
EC contribution:	€ 2 400 000
Duration:	36 months
Type:	STREP
Starting date:	1 January 2007
Project website:	www.fitbiotech.com

BACKGROUND

More than 40 million people worldwide are currently infected with HIV1. Most of those are from developing countries where there is an urgent need for efficient vaccine candidates. The HIV virus induces chronic infection in patients, eventually leading to deterioration of the immune system and the onset of immune deficiency. The right vaccine will be capable of inducing cell-mediated and humoral immunity against the virus and virally infected cells in different phases of the viral life cycle. This could be carried out by DNA vaccines if they can be made more efficient. Different technologies will be used to try to achieve this including the restricted expression of the multi-epitope/multivalent HIV antigens in specific cells of the epidermis; a micro-needle array-based infection device for reproducible and efficient delivery into the epidermis; and the adjuvant effect of different cytokines.

AIMS

EPIVAC aims to generate an effective and affordable DNA-based preventative and therapeutic vaccine against HIV. The first goal is the development of a reliable, reproducible and robust delivery system. The plasmids and genes used in these studies will allow for the quantitative evaluation of the efficiency and kinetics of delivery of plasmid DNA into the epidermis and epidermal cells.

The second goal of the project is to analyse the effect on the nature and extent of the induced immune response by different HIV1 antigen expression in different cells of the epidermis.

EXPECTED AND OBTAINED RESULTS

The expected results of the project are listed below:

- New devices and methodologies for DNA delivery to the epidermis.
- The generation of improved DNA-based vaccines.
- The generation of new proprietary HIV antigens based on the EPIVAC optimised vector.

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MUNANOVAC

MUCOSAL NANO-VACCINE CANDIDATE FOR HIV

Acronym:	MuNanoVac
Project number:	LSHP-CT-2006-037200
EC contribution:	€ 1 505 702
Duration:	36 months
Type:	STREP
Starting date:	1 January 2007
Project website:	www.munanovac.eu

BACKGROUND

There are many infectious diseases for which no vaccines are available, and there is no candidate that allows efficient T cell and B cell immune responses. In the case of HIV-1 mediated infection it is believed that both arms of the immune response (humoral and cellular) should be stimulated by any potential vaccine candidate. Recent data on natural primary HIV-1 infection has established that the spreading of the virus in the mucosa is essential for infection to take place. Therefore, every vaccination strategy should be able to elicit a strong mucosal immunity at the potential sites of contamination, and prevent spreading of HIV-1 virions.

AIMS

The MuNanoVac project will assess a new vaccine strategy to prevent HIV-1 infection based on a biodegradable synthetic colloidal carrier made of polylactic acid (PLA) nanoparticles covered with absorbed antigens. Such nanoparticle-based vaccine carriers allow targeting of dentritic cells or the transportation of the vaccine through skin or mucosal epithelial barriers. To amplify the mucosal immune response, the project will investigate the potential use of immunomodulator molecules co-adsorbed with HIV antigens onto PLA particles and will compare two different immunisation routes, mucosal or sub cutaneous, in different animal models.After selection of the best route of immunization associated with the more potent immunomodulatory molecules, two HIV-I antigens, trimeric gp140 (clade C) and p24 will be formulated onto PLA particles for assessing its efficacy as an HIV vaccine in non human primates.

MuNanoVac wants to demonstrate evidence that a strong and persistent mucosal immune response for a given antigen can be reached, using biocompatible PLA nanoparticles as a versatile vaccine vehicle.

EXPECTED AND OBTAINED RESULTS

MuNanoVac will contribute towards the following:

- bringing new knowledge and innovative technologies through the HIV vaccine discovery process;
- proposing new vaccine candidates using biodegradable synthetic colloidal carrier for combating and preventing HIV/AIDS.

In addition, the project's results will be used as a basis for developing biodegradable vaccine candidates for other poverty-related diseases.

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COMPUVAC

RATIONAL DESIGN AND STANDARDISED EVALUATION OF GENETIC VACCINES

Acronym: CompuVac
Project number: LSHB-CT-2004-005246
EC contribution: € 7 969 442
Duration: 48 months
Type: IP
Starting date: 1 January 2005

BACKGROUND

Recombinant viral vectors and virus-like particles are considered the most promising vehicles to deliver antigens in prophylactic and therapeutic vaccines against infectious diseases and cancer. Several potential vaccine designs exist but their cost-effective development lacks a standardised evaluation system.

AIMS

CompuVac's main objective is to set up a standardised approach for the rational development of genetic vaccines.

The process comprises the development of:

- a large panel of vaccine vectors representing various vector platforms and all expressing the same model antigens;
- standardized methodologies for the evaluation of T- and B-cell responses and of molecular signatures relevant to safety and efficacy;
- a database for data storage and analysis of large data sets;
- intelligent algorithms for the rational development of prime boost vaccination. One of our final goals is to generate and make available to the scientific community a "tool box" and an "interactive database" allowing the comparative assessment of future vaccines. We also aim to validate these tools by the rationale development of preventive and/or therapeutic vaccines against HCV.

A secondary objective is to apply these vectors, tools and methods to the development of a preventive and/or therapeutic vaccine against the hepatitis C virus (HCV) incorporating one or more of the platform vectors expressing the HCV envelope protein.

EXPECTED AND OBTAINED RESULTS

We have now assembled a unique set of vaccines of different class, from viral vector derived vaccines to inert VLPs, analysed their efficacy with standardised methodologies, and compared them with an intelligent database. This has already allowed us to make significant comparisons between different vaccine types and to initiate novel vaccine design and vaccination regimen. We are now evaluating prime-boost immunisation regimen with these vectors. We believe that this should have a significant impact on vaccine development, and notably for those vaccines requiring prime/boost immunizations.

As end products, the vector platform and gold standard tools, methods and algorithms will be available to the scientific and industrial communities as a toolbox and interactive database whose standardised nature should contribute to cost-effective development of novel vaccines.

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BACABS

ASSESSMENT OF STRUCTURAL REQUIREMENTS IN COMPLEMENT-MEDIATED BACTERICIDAL EVENTS: TOWARDS A GLOBAL APPROACH TO THE SELECTION OF NEW VACCINE CANDIDATES

Acronym:	BacAbs
Project number:	LSHB-CT-2006-037325
EC contribution:	€ 2 269 999
Duration:	36 months
Type:	STREP
Starting date:	1 January 2007
Project website:	www.bacabs.org

BACKGROUND

High throughput cloning and expression of large sets of genomic ORFs (open reading frames) has become a preferred industrial strategy for genome-wide searches of new vaccine candidates. For invasive infections in particular, the aim is to find proteins eliciting antibodies capable of binding to the bacterial cell surface and, through interaction with the complement system, effectively kill the bacteria. However, current data accumulating from reverse vaccinology studies indicate that only a small fraction of surface-exposed proteins appears to elicit antibodies with bactericidal activity.

Using information generated by reverse vaccinology projects the project will apply a novel multidisciplinary approach in identifying the structural requirements for viable bactericidal vaccine candidates, developing bioinformatics tools to predict compliance with such structural requirements. Therefore, a systematic analysis of sequence, structure, dynamics and interactions of selected protein targets will be undertaken; serogroup-B *Neisseria meningitidis*, a pathogen causing septicemia and meningitis, for which no effective vaccine exists, will be used as main model system.

AIMS

The aim of the project is to develop a strategy and tools to identify early in the vaccine development process those antigens that could induce production of bactericidal antibodies. To achieve this goal, the project is investigating the requirements for productive Ag-Ab-C1q complex formation, and is taking a multidisciplinary and comparative approach in studying the structural properties of a number of these complexes. The MenB vaccine development project of Novartis Vaccines & Diagnostics is being taken as a model and a source for useful data and reagent molecules.

EXPECTED AND OBTAINED RESULTS

- Structural information on a set of proteins that are components of the cell surface of major human pathogens
- Experimental protocols, bioinformatics tools and databases to assist antigen selection
- A framework in which integrated experimental and in silico methods for the study of macromolecular recognition can be further developed
- A web-based technological platform integrating the knowledge generated within the project and public external data relevant to vaccine development

Additional information, including updates on project results, may be obtained from the Project website:

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MICROBEARRAY

GENOME SCALE ANALYSIS OF THE IMMUNE RESPONSE AGAINST PATHOGENIC MICRO-ORGANISMS LEADING TO DIAGNOSTIC AND VACCINE CANDIDATES AND DEVELOPMENT OF AN INTEGRATED MICRO ARRAY PLATFORM FOR CLINICAL USE

Acronym: MICROBEARRAY
Project number: COOP-CT-2004-508399
EC contribution: € 1 401 002
Duration: 24 months
Type: NoE
Starting date: 21 June 2004

BACKGROUND

The genome sequences of microbial organisms responsible for diseases of worldwide medical importance have either already been sequenced or will be available in the near future. Technologies for producing large numbers of proteins have been developed and high-throughput assays, such as protein microarrays, have been clinically validated for detecting the presence of antibodies, in serum, directed against microbial antigens. These achievements provide the research sector with the opportunity to investigate the natural immune response against the whole proteome of a variety of micro-organisms. Powerful combinations of genomic information, molecular tools and immunological assays are becoming available to help identify the antigens that function as targets of protective immunity, or that could be used as markers for serodiagnosis.

AIMS

The project aimed to identify in micro-organisms of great medical relevance (*M. pneumoniae, C. pneumoniae, L. pneumophila, coronavirus spp and P. falciparum*) a large collection of surface and secreted proteins, as well as putative endotoxins. This protein repertoire was produced as recombinant molecules or as sets of overlapping synthetic peptides, and printed on array slides. The serum reactivity of groups of individuals with a proven history of exposure to the selected micro-organisms was analysed against the arrayed proteins, to identify diagnostic markers and correlates of protection.

EXPECTED AND OBTAINED RESULTS

This project significantly expanded the SMEs' bank of Intellectual Property and contributed to expertise within the RTD sector. It is anticipated that the proposed work in high throughput protein expression, software analysis, surface peptides synthesis, protein and peptide surface capture, and array reader instrumentation will create an integrated platform of great commercial and research value. Finally, MICROBEARRAY has contributed to unravelling how the humoral immune response interacts with the microbial proteomes, thus filling the gap between genomic data and development of novel vaccines and diagnostic tools.

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DEC-VAC

DEVELOPMENT OF A DENDRITIC CELL-TARGETED VACCINE AGAINST AIDS

Acronym:	DEC-VAC
Project number:	LSHP-CT-2005-018685
EC contribution:	€ 3 400 000
Duration:	48 months
Type:	IP
Starting date:	1 January 2006
Project website:	www.rubr-uni-bochum.de

BACKGROUND

Vaccines targeting dendritic cells (DCs) have been the topic of intense research on an international basis. The role of DC in virus-specific cellular immunity in HIV infection is particularly important, given the lack of neutralising antibody activity in AIDS patients. It is therefore likely that a DC-based anti-HIV vaccine could prove particularly efficacious against HIV/AIDS.

AIMS

The project aims to develop an innovative anti-HIV vaccine able to enhance uptake and presentation of antigens by dendritic cells (DCs). The project's strategy to enhance antigen uptake and presentation by DCs can be applied to protein vaccines, peptide vaccines, DNA vaccines and viral vector vaccines, thus providing a broad vaccination platform. Providing a novel HIV vaccine strategy for safety and efficacy studies in humans by the end of the project is an important aim. Therefore, the scientific and technological objectives are to determine the following for DC-targeted protein, DNA, and viral vector vaccines:

- the DC targeting efficacy;
- the immunogenicity;
- the efficacy of different adjuvants;
- the protective properties in the HIV-1/MuLV and SIV macaque model.

Based on these results, the mechanisms of protection are being investigated.

EXPECTED AND OBTAINED RESULTS

Given the striking positive results in rodent models, this strategy certainly has the potential to be effective and to confront the global emergency caused by the spreading HIV epidemic. Results from this research effort could lead to the development of a prophylactic or therapeutic HIV/AIDS vaccine. The DC-targeted vaccine approach could also be useful for the development of vaccines against other infectious diseases and cancer.

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DC-VACC

DENDRITIC CELLS AS NATURAL ADJUSTMENTS FOR NOVEL VACCINE TECHNOLOGIES

Acronym:	DC-VACC
Project number:	LSHB-CT-2003-503037
EC contribution:	€ 2 000 000
Duration:	36 months
Type:	STREP
Starting date:	1 January 2004
Project website:	www.biopolo.it/

BACKGROUND

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 (DCs) that rest until encountering foreign microorganisms or inflammatory stimuli. Early-activated DCs trigger innate immune responses that represent the first line of defence against invading pathogens. Activated DCs subsequently prime antigen-specific immune responses, clearing the infection and giving rise to immunological memory.

AIMS

The project's aims were to:

- develop novel vaccine technologies. Early clinical trials indicated that antigen-pulsed DCs have great potential for treating cancer. In *situ* DC targeting was developed for use as vaccines in infectious diseases and cancer;
- create tools and methodologies for the development of DC vaccine technology, including construction of viral and bacterial vectors, modification of RNA, peptides and proteins, and antibody development for targeting of the DC receptor repertoire. A comparison was undertaken for peptides, proteins, RNA, DNA and antigen modifications that allow presentation via MHC molecules;
- define optimal reagents and protocols for maturation and activation of mouse and human DC *in vitro* for use in vaccination. The optimisation of protocols for both species was compared in order to facilitate information from preclinical models being transferred to clinical trials for future projects. The aim was to obtain a clear understanding of how DCs induce pro-inflammatory versus anti-inflammatory cytokines, chemokines and their receptors, and how they activate CD4+ and CD8+ T cells. It was essential that such activation signals were tested for their ability to process and present antigen to T cells, leading to a protective Th1 response.

EXPECTED AND OBTAINED RESULTS

The project developed new adjuvants, targeting molecules and methodologies for enhancing anti-tumour therapies and interventions, plus vaccinations for infectious diseases

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THERAVAC

OPTIMISED DELIVERY SYSTEM FOR VACCINES TARGETED TO DENDRITIC CELLS

Acronym: THERAVAC
Project number: LSHB-CT-2004-503582
EC contribution: € 2 267 000
Duration: 54 months
Type: STREP
Starting date: 1 March 2004

BACKGROUND

Novel immunotherapies are urgently required for cancer and chronic infections as well as for prophylactic vaccination. In response to this need, optimised delivery systems for vaccines targeting dendritic cells are being developed and clinically evaluated in this project. Its approach relies on two new antigen delivery vectors: the detoxified adenylate cyclase toxoid (ACT), and the porcine parvovirus-like particles (PPV-VLP). They have been shown to target dendritic cells efficiently and specifically, allowing for a highly effective presentation of delivered antigens to T cells. These vaccine vectors enable the induction of strong, specific and protective immune responses.

AIMS

The project's aims are as follows:

- production of a GMP batch of ACT carrying the melanoma tyrosinase epitope suitable for a phase 1/2 clinical trial;
- the detailed toxicology assessment of this GMP batch of ACT;
- a phase 1/2 clinical trial in melanoma patients of this GMP batch of ACT carrying the tyrosinase melanoma $CD8^+$ T cell epitope;
- the understanding of the interaction of ACT with dendritic cells at molecular and atomic details;
- the detailed understanding of the mechanism of PPV-VLP specificity and efficacy;
- the engineering of improved vaccine delivery molecules based on the improved understanding of their functional mechanism.

EXPECTED AND OBTAINED RESULTS

The expected results of the project include:

- discovery of a novel mechanism of calcium mobilisation into myeloid cells by ACT which was shown to be linked to AC domain translocation across cytoplasmic membrane of cells;
- important progress in understanding the mechanisms underlying ACT interaction with CD11b, signalling activity on myeloid cells and the capacity to deliver the AC domain with antigens into cells. This was efficiently used to manipulate the antigen delivery potency of toxoid forms of ACT;
- significant development made in the understanding of how PPV-VLPs interact with dendritic cells. Importantly, these VLPs were shown to possess a strong adjuvant activity. The project has demonstrated that the baculovirus (BV) is responsible for this adjuvant effect and that it plays a major role in the strong immunogenicity of PPV-VLPs produced in the baculovirus-insect cell expression system. This adjuvant behaviour of BVs is mediated primarily by IFNα/β, although mechanisms independent of type I interferon signalling are also involved.

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AIDS-COVAC

GENERATION OF A CORONAVIRUS-BASED MULTIGENE AIDS VACCINE AND EVALUATION IN A PRECLINICAL SIV MODEL

Acronym:	AIDS-CoVAC
Project number:	LSHP-CT-2006-037416
EC contribution:	€ 958 000
Duration:	24 months
Type:	STREP
Starting date:	1 December 2006
Project website:	www.lfa-sg.ch

BACKGROUND

HIV infection represents one of the major health threats in the developing world, with millions of infected people suffering from immunosuppression-associated diseases, such as opportunistic infections or infection-associated cancer. Treatment with multiple highly-efficient anti-HIV drugs is affordable in more industrialised countries only. However, less developed countries, mainly in Africa, require a cost-effective vaccination strategy to prevent the further spread of the infection.

Coronaviruses spread via mucosal surfaces and can infect dendritic cells (DCs). These features and their exceptional transcription strategy make them extremely promising candidate vaccine vectors for overcoming known problems of current HIV vaccine approaches. This project is pursuing research in the murine coronavirus system, and seeks to further promote this specific line of research in Europe in order to pave the way for the generation of coronavirus-based HIV vaccines in humans.

AIMS

The project's aims are as follows:

- to develop a coronavirus-based multigene vaccine that specifically targets DCs;
- to evaluate the novel approach through preclinical testing in a simian model;
- to expand the understanding of the molecular biology of coronavirus and DC interaction, and exploit this knowledge to improve the novel virus vector system.

EXPECTED AND OBTAINED RESULTS

The following results are anticipated:

- new devices and modalities for DNA delivery to the epidermis;
- a generation of improved DNA-based vaccines combining the advantages of GTU vectors for long-term expression and plasmo-VLP (virus-like particle) vectors for the presentation of antigens onto VLPs;
- generation of new proprietary HIV antigens based on the EPIVAC optimised vector.

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HIVAB

GENERATION OF BROADLY CROSS-NEUTRALISING ANTIBODIES FOR INNOVATIVE ACTIVE-PASSIVE HIV VACCINATION STRATEGIES BASED ON MODIFIED IG-GENE TRANSGENIC MICE

Acronym: HIVAB
Project number: LSHP-CT-2005-019052
EC contribution: € 950 000
Duration: 24 months
Type: STREP
Starting date: 1 December 2005

BACKGROUND

Neutralising antibodies could contribute significantly to antiretroviral treatment and vaccines so as to improve protection from HIV infection acquired during birth or through accidental exposure to the virus. Only a few antibodies with broad cross-clade neutralising properties are available in the field of HIV applied research: b12, 2G12, 2F5 and 4E10. They recognise either epitopes presented only transiently during infection of cells, or epitopes not recognisable by unmodified immunoglobulins (2G12).

While strong interest has emerged in the development of immunogens or immunisation technologies capable of eliciting 2F5-like Abs by immunisation, the neutralising activity of 2F5 has not been recapitulated by administering either gp41, gp160, or a variety of immunogens including the 2F5 core epitope in different contexts. The importance of residues flanking the recognition sequence in binding 2F5 has been revealed, which could explain the inability of some, but not all, of the immunogens tested to induce neutralising Abs.

AIMS

The project's aims were as follows:

- to develop transgenic mice with distinct genetic alterations;
- to develop antigens based on synthetic HIV envelope genes;
- to identify and later produce novel neutralising antibodies following humanisation.

This project used two experimental strategies, separately and in combination: the first was used to produce mice with germ line-modified immunoglobulin genes, which introduce extended mobility into the immunoglobulin protein backbone; the second used HIV receptor-transgenic mice for immunisation, to favour receptor mediated transitory stages of the viral envelope.

EXPECTED AND OBTAINED RESULTS

The project anticipates the following results:

- better control of HIV infection in humans;
- transfer of results into biotechnological applications;
- recognition of immunogens from various sources (to date, steric constraints have hindered recognition).

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INNOVAC

HIGHLY INNOVATIVE STRATEGIES FOR VACCINATION TO POVERTY-RELATED DISEASES

Acronym:	INNOVAC
Project number:	LSHP-CT-2006-036871
EC contribution:	€ 2 000 000
Duration:	36 months
Type:	SME-STREP
Starting date:	January 2004
Project website:	www.rhul.ac.uk/Biological-Sciences/AcademicStaff/Cutting/cutting.html

BACKGROUND

Between one and two million people die of malaria and more than 300 million are infected with it every year, mainly in Sub-Saharan Africa. Strategies for developing malaria vaccines have been targeted at specific points in the parasite life cycle during which the organism appears particularly susceptible to the host's immune system. Preventing infection is now especially important because resistance to anti-malarial drugs is growing.

Tuberculosis (TB) poses a similar threat to malaria in its ability to cause devastation. This disease, thought almost extinct only a decade ago, is now making a resurgence, partly fuelled by the mycobacterium's growing resistance to drug therapy. Over one third of the world's population has been exposed to the TB bacterium and new infections occur every second throughout the world. One in 10 people carrying the virus will develop the full symptoms.

AIMS

The project's aim was to develop three platform technologies that were used for developing innovative methods of vaccination against tuberculosis (TB) and malaria. The research platforms included:

- bacterial spores — robust and heat-stable bioparticles with proven efficacy as mucosal vaccines;
- intracellular and invasive bacteria including *E. coli* strains and *Mycobacterium bovis* (rBCG);
- S-layer protein conjugates and S-layer protein coated liposomes.

The project tested and evaluated vaccination strategies using recombinant systems, some in their infancy and others at a more advanced stage of development. This included construction of vaccine vehicles, their evaluation in animal models, challenge experiments and safety tests, where appropriate, in order to bring potential vaccines to the clinical evaluation stage.

EXPECTED AND OBTAINED RESULTS

The project seeks to achieve the validation of one or possibly more of the platform technologies in development. Encouraging results from one or more vaccine candidates against either malaria or TB could lead to preclinical studies and long-term, clinical studies in collaboration with industrial partners.

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IMMUNOGRID

THE EUROPEAN VIRTUAL HUMAN IMMUNE SYSTEM PROJECT

Acronym:	ImmunoGrid
Project number:	IST-2004-028069
EC contribution:	€ 1 950 000
Duration:	36 months
Type:	STREP
Starting date:	1 February 2006
Project website:	www.immunogrid.org/

BACKGROUND

The human immune system is composed of a complex system of specialised cells and organs that work together to find and kill invaders. It is responsible for distinguishing the foreign proteins of invading pathogens and for protecting against alien substances and infections. It can reject transplanted organs, but it is also susceptible to attack itself, from HIV in particular.

Leading European experts in computational immunology are developing a virtual immune system known as the ImmunoGrid to model the human immune system. The ImmunoGrid project is developing separate simulators for different pathological conditions. At present, the simulator works mainly at cellular level, but the partners are developing it to simulate whole organs. The complexity of the immune system, and the fact that the most successful pathogens each have their own unique way of overcoming defences, means that a single simulator cannot be developed for the whole immune system.

Computer simulation will help understand the host immune response to attacks by pathogenic bacteria and viruses. It will also enable researchers to assist in the treatment of cancers of the immune system, such as leukaemias and lymphomas.

The ImmunoGrid applications will provide tools for clinicians and vaccine/immunotherapy developers, for identification of optimal immunisation protocols. The unique component of the project is that it aims to connect molecular level interactions (which regulate immune responses) with system level models (which study behaviour of the immune system as a whole) — a novel approach to disease prevention and treatment.

AIMS

The project's aims are as follows:

- to construct a database of information regarding all aspects of the immune system;
- to develop new techniques for modelling critical intermolecular interactions in the immune system;
- to test different regimes for vaccine administration in the treatment of mammary tumours in mice.

EXPECTED AND OBTAINED RESULTS

The project anticipates the development of a virtual immune system to aid drug development for cancer and HIV.

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VACCTIP

VACCINE STRATEGIES FOR COMBINED TARGETING OF INNATE AND ADAPTIVE IMMUNE PATHWAYS

Acronym:	VaccTIP
Project number:	LSHP-CT-2004-012161
EC contribution:	€ 1 000 000
Duration:	24 months
Type:	STREP
Starting date:	1 May 2005
Project website:	www.mtc.ki.se/groups/liljestrom/VaccTIP/index.html

BACKGROUND

Most candidate vaccines for HIV-1 are designed to stimulate cell-mediated immune responses, but results show that these responses are unlikely to be sufficient for protection. Current HIV-specific candidate vaccines are mainly aimed at targeting cellular immunity and have a limited immunogenicity restricted to a few epitopes. Therefore, new vaccines that stimulate stronger and broader T cell responses, as well as neutralising antibodies need to be developed. Recent advances emphasised the key role of innate immunity pathways in the stimulation of effective adaptive immune responses. VaccTIP assessed different approaches that activated the innate immune system in order to selectively trigger, enhance and shape cellular and humoral neutralising responses.

AIMS

The project aimed to:

- produce polymeric CD40L (Mega-CD40L) and bacterial Flagellin as two novel adjuvants targeting the innate and adaptive immune pathways;
- construct novel alphavirus-based vaccine vectors which stimulate innate immunity and further elevate humoral and cellular immune responses, and to bring technology forward in view of future implementation as global vaccines in developing countries;
- analyse innate immune reactions both in human and murine settings;
- evaluate the effect on T and B cell responses to specific antigens in human and murine models;
- evaluate the adjuvanticity on recombinant alpha- and poxvirus vectors expressing HIV-1 antigens.

EXPECTED AND OBTAINED RESULTS

VaccTIP anticipated the development of an effective HIV vaccine which requires the generation of both humoral (neutralising antibodies) and cellular immunity. Specific clinical candidates were not developed in the framework of the consortium, however, significant steps were made towards achieving the overall objectives even after the end-date of the project.

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MVACTOR

HOST IMMUNE ACTIVATION-OPTIMISED VACCINIA VIRUS VECTORS FOR VACCINE DEVELOPMENT

Acronym:	MVACTOR
Project number:	LSHP-CT-2006-037536
EC contribution:	€ 1 000 000
Duration:	24 months
Type:	STREP
Starting date:	1 January 2007
Project website:	www.pei.de

BACKGROUND

Poxviruses engineered to express foreign genes are recognised as potent delivery systems for heterologous antigens and as candidate vaccines against a wide spectrum of human and animal diseases. One of these vectors, the safety-tested highly attenuated modified vaccinia virus Ankara (MVA) (a product of European vaccine research), serves worldwide as the vaccinia virus strain of choice for clinical investigations in experimental vaccination against AIDS, tuberculosis, malaria or tumour diseases. At present the MVACTOR consortium represents the only European research network with prime expertise in poxvirus research. Recent work by the project partners significantly increased the knowledge based on versatile poxvirus gene functions, so as to regulate virus-host interactions and to modulate innate and adaptive host cell immune responses.

With this project, MVA will serve as the basis to develop a new generation of potent viral vector vaccines with optimised host immune activating properties. Specifically, the projects focus is to identify and/or inactivate MVA gene functions that have immune inhibitory potential (e.g. counteracting interferons, interleukins, CC chemokine functions) and potentiate vector vaccine performance by virion modification and host cytokine co-expression.

AIMS

The project aims on the development of new generation potent viral vector vaccines with optimised host immune-activating properties based on the highly attenuated modified vaccinia virus Ankara (MVA). Specifically, it will identify and characterise MVA gene functions that have unknown and/or potentially specific immune inhibitory capacity. Basing on these results, it will then potentiate vector vaccine performance by rational genetic engineering of the MVA vector through:

- precise inactivation of viral immune evasion genes;
- specific activation of host innate immune responses;
- potent presentation of target antigens by APCs;
- selective expression of host adjuvant genes.

EXPECTED AND OBTAINED RESULTS

The project will derive state-of-the-art, second generation, safe and optimised MVA vectors with superior immunogenicity and enhanced protective capacity for use in future clinical evaluation of new candidate vaccines against infectious and tumor diseases.

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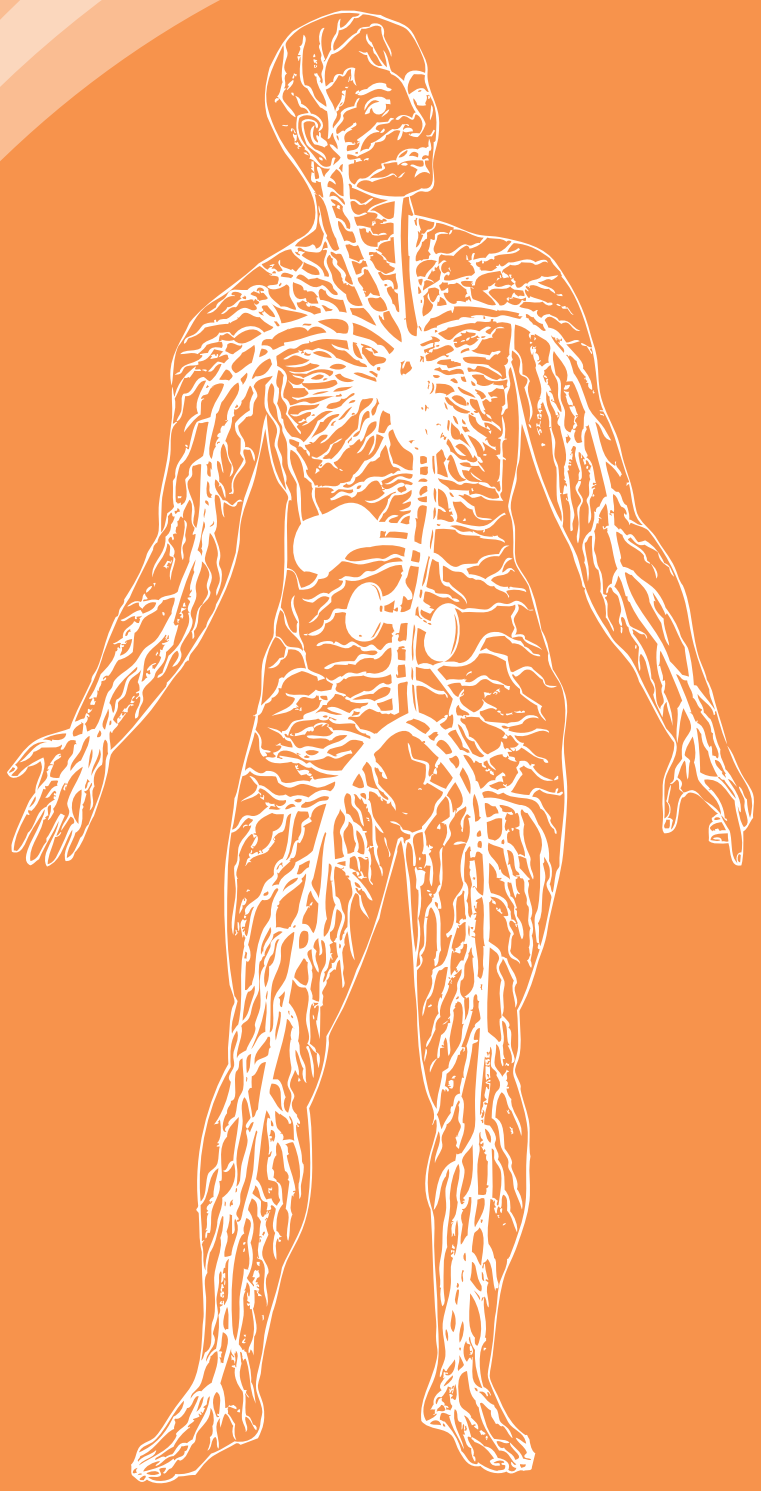
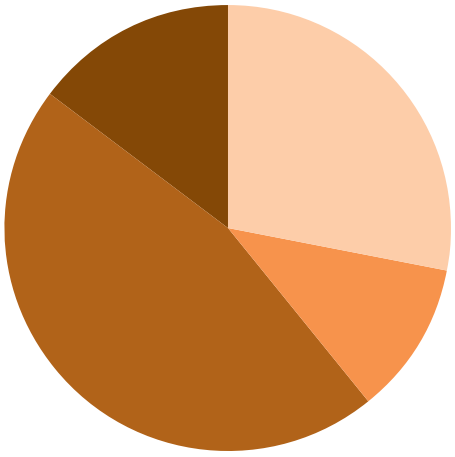
DISEASES SPECIFIC VACCINE RESEARCH



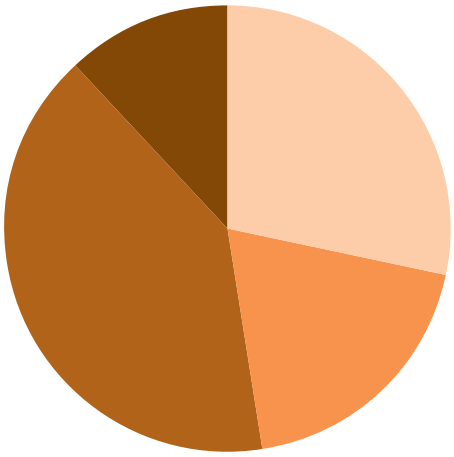
DISEASE SPECIFIC VACCINE RESEARCH

Funding of translational research has been a priority for the EC in the course of FP6, and the bulk of vaccine research activities has been projects that are tightly associated with a single disease or pathogen. During the 4 years of FP6, a total of 42 disease specific collaborative projects were funded with a total budget of EUR 136 million. The projects involved more than 300 research groups from all over Europe, as well as many non-European countries. The projects covered diseases that can broadly be classified into four different groups.



Budget Total = €136,029,199

- Non-infectious Diseases (€19,836,426)
- Poverty Related Diseases (€62,659,731)
- Neglected Infectious Diseases (€15,006,020)
- Emerging Epidemics (€38,527,022)



Number of Projects Total = 42

- Non-infectious Diseases (5)
- Poverty Related Diseases (17)
- Neglected Infectious Diseases (8)
- Emerging Epidemics (12)

POVERTY-RELATED DISEASES (HIV/AIDS, MALARIA AND TB)

The three major communicable diseases (HIV/AIDS, malaria and tuberculosis) account for nearly 18% of the disease burden in the poorest countries and for over 6 million deaths per year worldwide. Vaccines and treatments to combat these poverty-related diseases (PRD) have been slow to emerge for several reasons, including the huge scientific challenges involved. The combat against PRD is an established priority within the European Commission[1], and a major component of FP6 was been earmarked to vaccine research in this area. Vaccine research has been supported for all three PRDs, but more than half of all projects were focused on HIV/AIDS, thereby indicating the huge challenges for vaccine research in this particular area. For each of the 3 diseases, a major integrated project has received EC funding of more than EUR 10 million during a 5 year period to assemble a critical mass of diverse scientific excellence to undertake major translational research activities. The AVIP consortium comprises 20 research groups from Europe and Africa with an aim to generate novel AIDS vaccine candidates, based on combinations of HIV regulatory (Tat

1 COM(2005) 179 of 27.04.2005 FROM THE COMMISSION TO THE COUNCIL AND THE EUROPEAN PARLIAMENT: A European Programme for Action to Confront HIV/AIDS, Malaria and Tuberculosis through External Action (2007-2011)

and/or Rev, and/or Nef) and structural (Env and/or Gag/Pol) proteins. The largest EC-funded project to identify and develop malaria vaccines is EMVDA. EMVDA works with SMEs, European malaria vaccine research centres, the European Malaria Vaccine Initiative (EMVI) and the African Malaria Network (AMANET) to select the best malaria vaccine candidates among a portfolio of new 'engineered and improved' synthetic antigens. The main EC funding to TB vaccine development in FP6 was channeled through the TB-VAC consortium. TB-VAC joined 33 European institutions from 9 European and 4 African countries, and also included a major vaccine manufacturer. The project covers pre-clinical and early clinical development of both subunit and new, improved BCG vaccines.

EMERGING EPIDEMICS

Influenza pandemics such as the Spanish flu of 1918 to 1919, which killed between 50 and 100 million people around the world, is a reminder that new viral diseases can suddenly appear or re-appear with short notice and dramatic consequences for global public health. A newer example stems from spring 2003, when a hitherto unknown infectious disease, SARS (Severe Acute Respiratory Syndrome), was reported in China, and quickly spread to Hong Kong, Taiwan, Singapore, Vietnam and Canada before it was contained. The EC has acknowledged the importance of vaccine research in emerging infectious diseases by supporting a number of activities in this area. The largest number of projects is focused on pandemic influenza, thereby reflecting the current shortcomings of available flu vaccines. The main challenge is that flu virus changes so rapidly that vaccines formulated against one strain may be ineffective the following year. The largest EC project to address this is FluVacc, which is developing an improved technology for quickly producing new live attenuated influenza vaccines based on reverse genetics.

The other large integrated project in emerging epidemics is Hepacivac, which aims to develop prophylactic and therapeutic vaccine candidates that can elicit a strong and specific T cell response against the hepatitis C virus. There are around 170 million chronic hepatitis C virus carriers – about 3% of the world's population. Around 25 000 people are infected every year, mostly young adults who contract the virus through either intravenous drug use or sexual contact. No vaccine has yet been developed and the available antiviral therapy only works in a few patients. Hepacivac is focusing on the development of two Hepatitis C vaccine candidates. The first uses gene-based encodes for the 2000 amino acid-long HCV Non Structural region (from NS3 to NS5B) and using adenoviral vectors for delivery. The second consists of the recombinant HCV glycoproteins gpE1 and gpE2 associated to resemble a pre-virion envelope structure.

Besides influenza and hepatitis C, vaccine research for possible vaccines against SARS has also been funded by the EC as part of vaccine research for emerging epidemics.

NEGLECTED INFECTIOUS DISEASES

Neglected infectious diseases (NIDs) receive little attention from the media and public in comparison with "high profile" diseases such as HIV/AIDS, malaria and TB, but their effect can be just as devastating. NIDs are a highly diverse group of infectious diseases, including protozoal, bacterial, viral and helminth infections. They include some of the most common chronic infections among the world's poorest people, and they are responsible for millions of disabilities and deaths every year.

The EC has been supporting vaccine research in neglected infectious diseases during successive framework programmes since the early 1980s. Under FP6, it has funded a number of projects that are addressing such diverse topics as vaccines against diarrhoeal diseases caused by rotavirus (HEVAR), lyme disease (BOVAC) and potential vaccine approaches for helminth infections (TRANCHI). The EC funded vaccine projects for neglected infectious diseases are mostly STREP projects with an EC contribution between EUR 1 million and EUR 2 million for a project period of two years or less. However, as they are addressing infectious diseases that are otherwise neglected, many of the projects are expected to have an

impact in terms of societal value that supersedes their financial magnitude.

NON-INFECTIOUS DISEASES

The possibility of creating vaccines for a host of non-infectious diseases such as cancer, neurodegenerative diseases and autoimmune diseases provides one of the most exciting fields for current vaccine research. It holds the potential to meet a huge unmet medical need for some diseases, while for other diseases it may provide a future alternative to traditional treatments that often are costly, only partially effective and sometimes associated with several adverse effects. With the exception of a vaccine project against Alzheimer's disease (MIMOVAX), EC efforts in this area have been concentrated on cancer vaccines. The projects address identification of specific tumour antigens that are present in cancer cells, such as in leukaemia, and thereby provide potential immune targets for which immunogenic vaccines may possibly be designed. Other projects are targeting some of the major cancer types, such as melanoma, carcinoma, and lung cancer. This includes the CANCERIMMUNOTHERAPY consortium, which comprises 22 partners that have received a total EC contribution of EUR 12 million to develop a safe and efficient therapeutic vaccine against cancers such as melanoma. This will initially be done by comparing the effect of various types of vaccines, such as peptides and RNA with different types of immunological adjuvants and DCs. The field of vaccines for non-infectious diseases is highly promising, but it should be kept in mind that there are still many roadblocks to be overcome. Some of the basic discoveries and necessary technologies may not yet be sufficiently matured. As such, some of the EC funded activities in basic vaccinology will undoubtedly also benefit the future advancement of vaccines for non-infectious diseases.

AVIP

AIDS VACCINE INTEGRATED PROJECT

Acronym:	AVIP
Project number:	LSHP-CT-2004-503487
EC contribution:	€ 10 300 000
Duration:	72 months
Type:	IP
Starting date:	1 February 2004
Project website:	www.avip-eu.org/

BACKGROUND

Vaccines based on viral structural products (Env/Gag/Pol) alone have failed to prevent infection by Human Immunodeficiency Virus (HIV)/Simian Immunodeficiency Virus (SIV). New strategies have recently been developed aimed at blocking virus replication and onset of HIV/SIV in the absence of sterilising immunity. Control of virus replication may modify the virus-host interaction, favoring the host immune response, providing protection from disease progression and reducing virus transmission to healthy individuals. This strategy, useful for both preventive and therapeutic interventions, should include both nonstructural and structural viral products, since vaccines targeting viral structural products (Env/Gag/Pol), as well as viral regulatory gene products (Tat/Rev/Nef), should be superior at inducing immune responses to both early and late viral products.

AIMS

The aims of the project are:

- to generate novel HIV-1 vaccine candidates to be tested in phase I preventive and therapeutic trials in Europe within the five-year programme. To achieve this goal, four novel vaccines have been selected from a larger pool based on two criteria: the combination of HIV regulatory (Tat and/or Rev, and/or Nef) with structural (Env and/or Gag/Pol) genes/products, and the advanced stage of development of single components, including efficacy studies in monkeys and new murine efficacy models;
- to conduct parallel preventive and therapeutic phase I trials in Europe with the four novel combined vaccines;
- to perform feasibility studies and technology transfer in Developing Countries (DCs) for phase II/III trials;
- to carry out training in EU and in DCs through the "AVIP International School";
- to ensure community involvement both in EU and DCs.

EXPECTED AND OBTAINED RESULTS

- Development of vaccines based on the combination of regulatory and structural genes.
- Demonstration of the safety of the immunogenicity of the vaccine candidates through preclinical studies (mice and monkeys). For some of them (Tat±ΔV2Env and HIV-1 multigene approach) the protective efficacy was also successfully demonstrated in preclinical efficacy animal models (mice and monkeys).
- Clinical trials (preventative or therapeutic) for some vaccine candidates (HIV Tat clade B, HIV ΔV2 Env clade B, MVA-HIV Nef clade B, multi-HIV antigens/epitopes clade B, HIV multigene clade B) have been already performed or started in the past year. New phase I and II clinical trials (Multi-HIV antigens/epitopes multiclade vaccine; HIV multigene clade A, B, C vaccine; Tat clade B combined with HIV ΔV2 Env clade C vaccine) are expected to start during the year 2008. Recently, two new partners joined AVIP Consortium, the Ndlela vaccine site (p18) in South Africa and the NRL-Mbabane vaccine site (P19) in Swaziland. Cooperation with DCs for building up the capacity of potential vaccine clinical sites and upgrading local infrastructure is in place. Standardisation of techniques and procedures are ensuring reproducibility of all results.
- Training in all AVIP activities, both in the EU and in DCs is ongoing. The main instrument for the training activity is the AVIP International School, which has been created by joining existing centres in the EU and South Africa. Many of the assays and other aspects of the phase I trials will be used in future phase II and III trials in South Africa and Swaziland and the participation of South African and Swazi researchers will promote continuity in the development of the vaccines.
- Exploitation of synergies with national and international ongoing programmes, such as the Italian Concerted Action on HIV/AIDS Vaccine development (ICAV) and the Swedish International Development Cooperation Agency (SAREC/

SIDA). The project also has bilateral programmes with Europe and DC, such as the HIV Incidence Study (HIVIS-INCO-FP6), the Very Innovative AIDS Vaccine (VIAV-STREP-FP6), the Mucosal Vaccine Approaches for Poverty Related Diseases (MUVAPRED-IP-FP6), the European Vaccines and Microbicides Enterprise (EUROPRISE-NoE-FP6), the Standardization of HIV Neutralization Assays to be Used in Vaccine Research and Clinical Trials (NEUNET-SSA-FP6).

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RMVHIV

RECOMBINANT MEASLES VIRUS AS A VECTOR FOR HIV VACCINES

Acronym: RMVHIV
Project number: LSHP-CT-2005-019043
EC contribution: € 5 500 000
Duration: 49 months
Type: IP
Starting date: 1 January 2006

BACKGROUND

This project aims at demonstrating the safety and immunogenicity of a novel recombinant measles virus (MV) vector for use as an AIDS vaccine. The vector is replication competent *in vivo* and is derived from a widely used measles vaccine strain (Schwarz), which is known to induce very long-lasting immunity. This novel vector potentially offers a unique combination of safety and potency. The recombinant HIV MV vectors will express three relatively conserved HIV proteins (i.e. Gag, Pol, Nef) from HIV clade B and A strains. A Good Manufacturing Practices (GMP) compatible production process for the recombinant MV vector will be developed and a GMP lot will be produced for two clinical studies.

The first study will evaluate the safety profile of the MV vector, while the second study will also assess the immunogenicity in MV-immune volunteers. With these two clinical studies, the project will specifically address potential shedding of the recombinant vector into the environment and the potential negative impact of pre-existing MV immunity.

The measles vaccine, a live attenuated strain of MV, is one of the safest human vaccines available and has been given to billions of children since the 1960s. However, because of the inadequate distribution of the vaccine in developing countries, there are still 45 million cases of measles and 800 000 child deaths per year worldwide.

The Pasteur Institute has developed an MV vector based on the Schwarz strain, the safest and most widely used vaccine strain. The consortium is proposing to construct recombinant MV vectors that express the HIV-1 clade B and A Gag, Pol, and Nef proteins. These proteins possess highly conserved regions that have been shown to be the target of CD8-positive cells, and thereby constitute a promising antigenic composition for an HIV vaccine. It has been demonstrated that CD8-positive cells from individuals infected with virus strains from different clades are highly cross-reactive with respect to the Gag, Pol, and Nef proteins. By assuming a similar cross-reactivity for vaccine-induced immune responses, RMVHIV is based initially on HIV clade B antigens. The choice of clade B antigens will also allow for subsequent combination vaccine regimen using GSK's clade B adjuvanted protein vaccine.

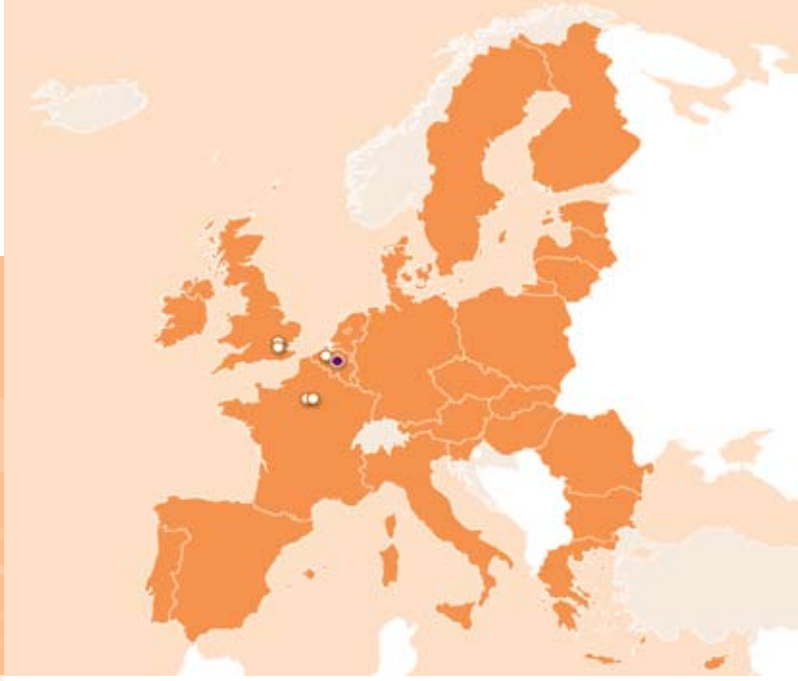
AIMS

The objective of RMVHIV is the demonstration of safety and immunogenicity of a recombinant HIV MV vector in adult HIV-uninfected volunteers. This includes the identification of a suitable dose of recombinant MV, the demonstration of an acceptable reactogenicity profile, and the characterisation of potential virus shedding. Furthermore, the vaccine will have to induce significant levels of HIV-specific CD8-positive cells in volunteers with pre-existing immunity, and ideally also measurable CD4-positive cell and antibody responses.

EXPECTED AND OBTAINED RESULTS

The project has defined a mostly sequential development path. The first stage is the construction and characterisation of recombinant MV expressing HIV clade B Gag, Pol, and Nef proteins. The characterisation includes the evaluation of immunogenicity in mice, established growth characteristics in a production cell line and analysis of genetic stability. Based on these results, a corresponding HIV clade A MV vector will be developed and compared to the clade B vector in a monkey immunogenicity study.

The consortium will assess several parameters that are relevant for the development of a production process that is compatible with GMP manufacture. When a suitable HIV clade B MV vector is selected and a process has been established, a GMP clinical lot production will be initiated and the resulting material subjected to a formal QC release. The GMP material will also serve for toxicology studies in macaques in order to assess the reactogenicity, toxicity, biodistribution and shedding of the recombinant MV. The analysis of the GMP lots, the data from the toxicology study, and other supportive data will be compiled in a dossier for submission to regulatory authorities.



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AUTO/ALLO CELL-HIV

DEVELOPMENT OF A NOVEL THERAPEUTIC HIV-1 VACCINE: HORIZONTAL GENE TRANSFER BY USING APOPTOTIC HIV-1 DNA CONTAINING ACTIVATED T CELLS

Acronym:	AUTO/ALLO CELL-HIV
Project number:	LSHP-CT-2005-018953
EC contribution:	€ 1 700 000
Duration:	36 months
Type:	STREP
Starting date:	1 December 2005
Project website:	www.avaris.se/

BACKGROUND

HIV/AIDS has now killed more than 20 million people worldwide and over 40 million are living with the virus. It is continuing to spread and its worse casualties are in Africa where 2 million people are dying of it every year and 11 000 contract it every day. Progress has been made on HIV/AIDS research, but a suitable vaccine has not yet been found. Novel therapies and a successful prophylactic vaccine are urgently needed.

AIMS

The project has discovered that genes can be horizontally transferred to neighbouring cells by the uptake of apoptotic cells, which also allows transfer of proteins leading to cross-presentation of antigens. The aim is to develop a therapeutic HIV vaccine using apoptotic cells as the antigen delivery system. In order to achieve this the project is performing the following actions:

- carrying out safety and immunogenicity studies in macaques;
- optimising the techniques for production of AutoCell/AlloCell in a good management practice (GMP) certified Cell Therapy Centre;
- producing individualised prototype AutoCell/AlloCell compositions;
- launching a phase I/II clinical trial.

Anti-retroviral treatment leads to reconstitution of immune responses to many pathogens, but it does so without the emergence of HIV-specific responses. Anti-retroviral treatment also allows patients to respond to immunisation using recall antigens and neo-antigens. Hence, it may be feasible to induce a novel adaptive HIV-1-specific immune response by therapeutic vaccination, which would also allow the patient to stop anti-retroviral medication.

EXPECTED AND OBTAINED RESULTS

The study expects to obtain safety measurements and proof of concept in macaques. In addition, GMP compliant production protocols will be developed. If feasibility and efficacy in a therapeutic HIV trial can be shown, it will open up the possibility of applying the concept to a preventive HIV vaccine.

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POX-GENE

A COMBINED POX-VIRUS/ LENTIVIRAL VECTOR SYSTEM TO TREAT HIV INFECTION; IMMUNISATION AND DIRECT IN VIVO GENE TRANSFER IN T-LYMPHOCYTES

Acronym:	Pox-gene
Project number:	LSHP-CT-2005-018680
EC contribution:	€ 1 180 000
Duration:	36 months
Type:	STREP
Starting date:	1 December 2005
Project website:	www.bprc.nl

BACKGROUND

Despite its successes, it is clear that highly active anti-retroviral therapy (HAART) cannot eradicate HIV infection and that virus rebounds as soon as treatment is interrupted. In addition, HIV infection in humans induces chronic changes in the phenotype and function of CD4 and CD8 T-cells as well as dendritic cells, which are only partly restored after the initiation of HAART. In order to alleviate the permanent dependency on HAART, alternative therapies must be developed to restore normal immune function. Attenuated pox-viruses are currently under evaluation as prophylactic or therapeutic vaccines against AIDS.

This project exploits attenuated pox-viruses to develop a treatment that reinforces patients' immune response to HIV and simultaneously renders their T cells resistant to infection.

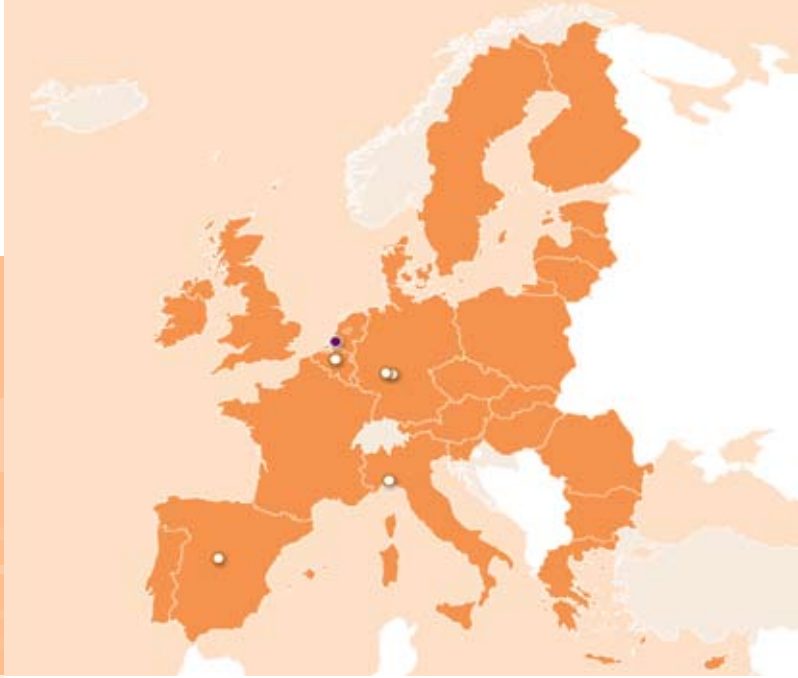
AIMS

The project aims to develop a combined vaccination/ gene therapy protocol for the treatment of HIV infection. Currently available technology for genetically modifying MVA pox-viruses was exploited to create a vector that expresses both HIV-1 proteins and an HIV inhibitory lentiviral construct. Target cells infected with MVA therefore express not only HIV-1 proteins capable of stimulating antigen specific T cells, thereby boosting anti-HIV-1 immune responses, but will also release lentiviral particles capable of transducing antigen stimulated T cells with an anti-viral gene that protects them from HIV-1 infection.

EXPECTED AND OBTAINED RESULTS

The expected results for this project are:

- the development of pox-gene vectors effective for antigen specific stimulation and transduction of T cells;
- the development of gene constructs that encode secreted HIV inhibitory peptides.



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ALLOMICROVAC

A COMBINED MICROBICIDAL-IMMUNISING STRATEGY AGAINST SIV AND HIV INFECTION

Acronym: Allomicrovac
Project number: LSHP-CT-2006-036928
EC contribution: € 1 100 000
Duration: 24 months
Type: STREP
Starting date: 1 January 2007

BACKGROUND

There are two known natural HIV-1 resistance states: alloimmunity and homozygous CCR5 mutation. The protein HSP70 is also found within the virion membrane of HIV-1 and functions as a chaperone during intracellular transport. HSP70 expression is significantly increased in lymphocytes from HIV-1 infected subjects.

There is a striking resistance to HIV-1 infection in homozygous Δ32 CCR5 mutation, found in about 1 % of caucasians. These individuals lack cell-surface expression of CCR5 generate a large amount of CC chemokines (CCL-3, CCL-4 and CCL-5) and may develop antibodies to CCR5, but they do not suffer from ill health. This project used the principle of potentiation, where a reagent enhances sensitisation to an antigen with regard to alloimmune, CCR5 and HSP70 responses.

AIMS

The project aims to utilise one cohort of macaques for three HIV-1/SIV preventive methodologies in microbicide, preventive and therapeutic immunisation. Macaques that are not infected are to be evaluated for preventive immunity; infected animals are utilised for therapeutic immunisation two months after infection.

Emphasis is on determining whether a trimolecular construct of MHC antigens combined with microbial HSP70 and extracellular CCR5 peptides can be utilised in microbicidal, preventive and therapeutic immunisation. Combining a short term microbicide with a long term preventive vaccine will deal with the problem of repeated applications of microbicides before sexual intercourse.

EXPECTED AND OBTAINED RESULTS

It is expected that in a proportion of macaques treated with the trimolecular construct infection will be prevented at the mucosal site of viral entry. As the construct is immunogenic, repeated applications will induce immune responses and memory to the vaccine components; this may prevent subsequent viral challenge. Thus, the microbicidal agent may also function as a preventive vaccine.

By early 2008, the HSP70-CCR5 construct for immunization was produced, consisting of dextramers of macaque MHC A1, A4 and A8 alleles and dextramers linked to HSP70 and CCR5 N terminal and loop 1 and 2 peptides. The final vaccine constructs was assembled in the molar ratio of 1 mol Dextran / 10 mol MHC / 8 mol HSP70CCR5-tripeptide. Two groups of macaques were treated vaginally by the dextramers MHC-HSP70-CCR5 peptide construct at 2-weekly intervals, followed 30min. later by 50TCID of SIVmac251. A 3rd group of macaques was treated with saline prior to treatment with SIVmac251 and a 4th was a naive control group. The macaques are monitored for innate immune factors, vaginal and serum antibodies, CC chemokines, cytokines and T cell functions. The investigation should be completed by the end of the year, when the results will be analysed and published.

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VIAV

VERY INNOVATIVE AIDS VACCINE

Acronym:	VIAV
Project number:	LSHP-CT-2004-012188
EC contribution:	€ 1 000 000
Duration:	24 months
Type:	STREP
Starting date:	1 January 2005
Project website:	www.iss.it

BACKGROUND

There are indications that the HIV Tat protein increase HIV cell absorption, infectivity and tropisms by interacting with components of the HIV membrane and envelope protein (Env). Because the interaction between Tat and Env is believed to increase the generation of complex-specific, neutralisation-sensitive epitopes and/or the stabilisation of cryptic and/or transiently exposed Env epitopes, a vaccine based on Tat-Env complexes was considered likely to generate protective immune responses against vulnerable viral targets.

AIMS

The intention of this project was to develop a highly innovative Tat-Env complex-based vaccine capable of inducing cross-clade neutralising antibodies against novel, neutralisation sensitive Env epitopes to prevent HIV infection and/or AIDS progression. This was achieved using new antigen design as a result of novel virological, immunological and modelling data from the VIAV consortium.

EXPECTED AND OBTAINED RESULTS

The project identified novel HIV/AIDS vaccine immunogens and formulations for inducing broad immunity against HIV. Tat Env complexes were characterised and used to immunise small animals. Neutralising antibody responses were also characterised and novel neutralisation-sensitive complex-induced epitopes identified.

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HIV VIROSOMES

DEVELOPMENT OF A NEW VACCINE AGAINST HIV: VIROSOMES INCORPORATING HIV PROTEINS

Acronym: HIV VIROSOMES
Project number: LSHP-CT-2004-012183
EC contribution: € 973 930
Duration: 36 months
Type: STREP
Starting date: 1 January 2005

BACKGROUND

Presently, only few broadly neutralizing antibodies against HIV-1 are known, two of those binding to sequences located within the membrane proximal external region (MPER) of the HIV-1 transmembrane glycoprotein gp41 (2F5 and 4E10). Numerous efforts have been undertaken to elicit 2F5- and 4E10-like antibodies, none has brought a major breakthrough. There is evidence that the lipid environment is required for full epitope recognition, which can be achieved by the use of liposomes. The ability of liposomal vaccines to raise humoral as well as cellular immune responses is desirable for an effective immunization against HIV-1. However, major drawbacks concerning the use of liposomes have been the cumbersome production methods with limited possibilities to control size distribution and antigen incorporation rates, denaturation of sensitive proteins, lack of scalability, high costs and difficulties to comply with regulatory requirements for human application.

AIMS

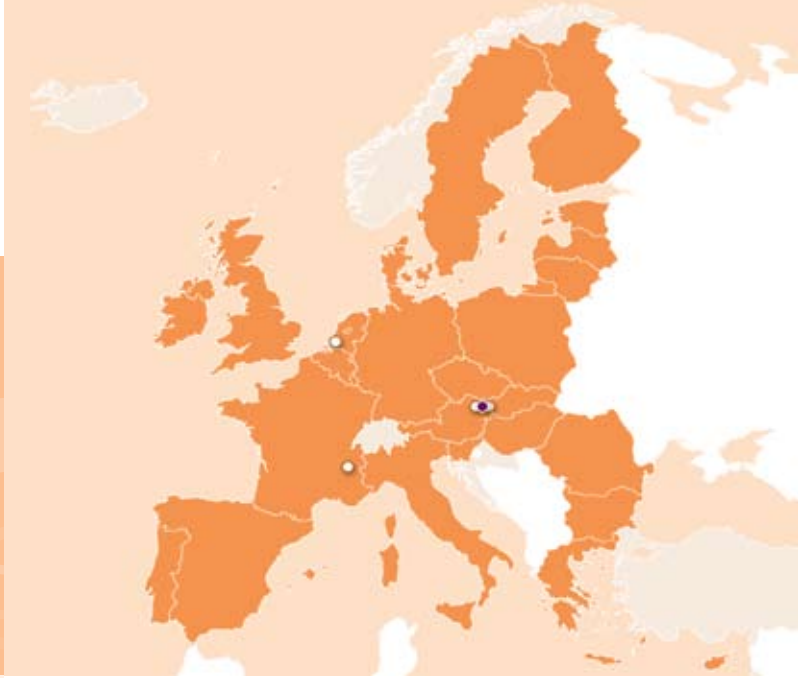
The objective of the project was to develop a preventive HIV vaccine using a focused straight-forward approach. The aim was to incorporate native proteins derived from primary HIV strains into liposomes generated by a novel large scale liposomal technology. Alternatively, recombinant HIV proteins should be used. This project included:

a. stabilisation of the native structure and conformation of native and recombinant HIV envelope proteins in liposomes
b. selection of candidate vaccines in small animal immunisation studies
c. establishment of immunogenicity, and eventually, efficacy in the rhesus macaque model
d. establishment of a GMP compliant process suitable for production of clinical material

EXPECTED AND OBTAINED RESULTS

To allow a fast-track development of the proposed vaccines the following tasks were pursued during the three project years:

- Generation of recombinant and primary virosomes (containing recombinant gp41 antigen or primary proteins)
- Characterisation of virosomes
- Safety testing of liposomal preparations
- Small animal immunisation studies
- Non-human primate studies
- Establishment of medium/large scale virosome production process



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TIP-VAC

EXPLAINING AND IMPROVING EFFICACY OF TARGETED IMMUNODEFICIENCY VIRUS-LIKE PARTICLE VACCINES AGAINST AIDS

Acronym:	TIP-VAC
Project number:	LSHP-CT-2004-012116
EC contribution:	€ 951 650
Duration:	24 months
Type:	STREP
Starting date:	1 January 2005
Project website:	www.ruhr-uni-bochum.de

BACKGROUND

Work on live attenuated immunodeficiency viruses in non-human primate models showed that a vaccine can provide protection from progression to AIDS. A number of effector mechanisms, including neutralising antibodies and CD8+ cytotoxic T lymphocytes, are likely to contribute to protection. A common feature of vaccination with recombinant viral proteins and whole inactivated viruses is injection of exogenous antigens, which predominantly leads to MHC-II restricted cellular immune responses and production of antibodies. Expression of antigens by cells of the vaccinees should lead to the presentation of antigens on MHC-I and MHC-II molecules. Therefore, DNA and viral vector vaccines have been studied extensively and depending on the stringency of the challenge system, various degrees of protection have been observed. Instead of using viral vector systems to induce MHC-I and MHC-II-restricted immune responses, a heterologous surface protein was incorporated into immunodeficiency virus-like particles, which should increase uptake and presentation of the exogenous viral antigens on MHC-I and MHC-II molecules. This might explain evidence for protection from disease progression in monkeys immunised with these targeted virus-like particles.

AIMS

The aims of the project were to:
determine the efficacy of the VLPs in a larger number of animals;

- understand better the requirements for and the mechanisms of protection;
- further improve the targeted VLPs.

The project developed a targeted immunodeficiency virus-like particle vaccine (VLP), which has a heterologous viral surface protein incorporated in the membrane of the particle. This should increase uptake and presentation of VLPs by dendritic cells. A pilot vaccination experiment in the SIV/macaque model provided strong protection against challenge with a pathogenic SIV.

EXPECTED AND OBTAINED RESULTS

The partners had expected to confirm vaccine efficacy in a larger number of animals, however the VLP vaccine that was tested did not result in a significant show of efficacy during a short vaccination regimen.

Furthermore, studies showed that CD8+ T cell responses were not sufficient to control viral replication. Overall, the project showed that VLP priming (and boosting with adenoviral vectors) could facilitate the induction of protective mechanisms such as the neutralizing antibody responses.

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EPI-VAC

IDENTIFICATION OF NOVEL EPITOPES AS HIV-1 VACCINES CANDIDATES

Acronym:	EPI-VAC
Project number:	LSHP-CT-2005-012168
EC contribution:	€ 911 050
Duration:	24 months
Type:	STREP
Starting date:	1 August 2005
Project website:	www.dbbm.unina.it

BACKGROUND

Despite the need for an effective HIV-1 vaccine, truly prophylactic candidates are not currently available. The current HIV-vaccine candidates tested to date, preclinically or clinically, have all failed to protect from primary infection and have afforded limited protection. The identification of immunogens eliciting broadly neutralising antibodies has hampered the efforts of researchers seeking to develop a truly prophylactic HIV-1 vaccine. This lack of significant cross-protection has fuelled concerns as to whether classical Env-based vaccines can afford enough protection against field isolates.

AIMS

This project aimed to select epitopes that mimic neutralisation-sensitive domains of HIV-1 envelope and may function as candidate HIV-1 vaccines and. It carried out the following strategies to meet its objective:

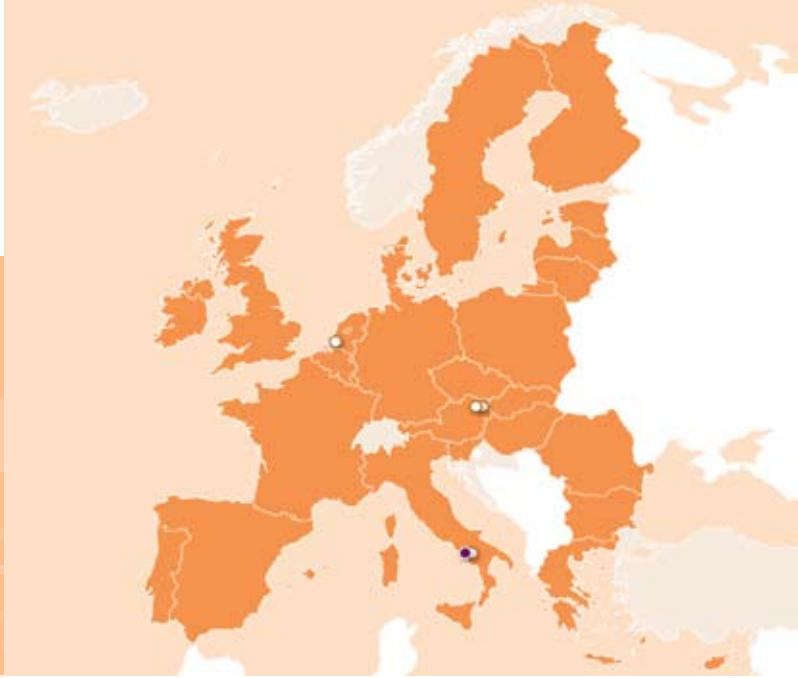
- screening of random peptide libraries with novel MAbs that neutralise primary HIV-1 isolates assigned to distinct clades;
- designing 30 to 40 amino acid peptides that mimic discontinuous regions of gp120 and gp41 that are sensitive to neutralisation by antibodies and are conserved among HIV strains of distinct clades.

In order to meet the challenge, EPI-VAC developed pools of innovative immunogens that mimic conserved regions of the viral envelope and are shared by a substantial percentage of primary viral isolates assigned to distinct clades from disease progression, if volunteers are exposed to heterologous isolates (1-3).

EXPECTED AND OBTAINED RESULTS

EPIVAC's results were as follows:

- development of novel vaccine candidates;
- optimisation of vaccine delivery;
- immunological evaluation of vaccine candidates in rodents.



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EMVDA

THE EUROPEAN MALARIA VACCINE DEVELOPMENT ASSOCIATION

Acronym:	EMVDA
Project number:	LSHP-CT-2006-037506
EC contribution:	€ 13 500 000
Duration:	60 months
Type:	IP
Starting date:	1 December 2006
Project website:	www.emvda.org

BACKGROUND

There is considerable optimism that a malaria vaccine can be developed. This is based on the fact that acquisition of immunity induced by natural infection does eventually prevent mortality and provide protection against clinical disease. There has been interest in the development of malaria vaccines for over 30 years, with the initial research emphasis on attenuated or killed whole organisms, and more recently on subunit-based approaches. The malaria parasite is a complex organism with an elaborate lifecycle; as a consequence much effort has been devoted to identifying molecules that stimulate host immunity and identifying protective components of that immune response. In parallel, research on delivery technologies has sought to develop ways to evoke protective immune responses by active immunisation.

Three stages of the malaria parasite lifecycle are targeted for vaccine development: the pre-erythrocytic, the asexual and the sexual blood stages. This project is very largely focused on the asexual blood stage that is responsible for the disease. This is the area in which European laboratories are probably most globally competitive, and it allows them to focus relatively limited resources to the greatest advantage. The project's strategy includes the development of new 'engineered and improved' synthetic antigens, for example with amino acid sequences from two or more antigens or with modifications to improve immunogenicity.

AIMS

The goal of the project is to systematically develop and test malaria vaccines by comparative and continuous evaluation of candidates. The best malaria vaccine candidates are being selected through collaborations with two SMEs, eight European malaria vaccine research centres, the European Malaria Vaccine Initiative (EMVI) and the African Malaria Network (AMANET). These vaccines will be developed further within a process that includes antigen validation, as well as the creation of a vaccine development rationale and early proof-of-principle clinical trials.

To develop a vaccine for malaria a scientific and technological structure supported by effective management has to be established in order to move candidate malaria parasite antigens through five stages of preclinical and clinical testing. Individual candidates are at different stages of development. Stringent go/no-go criteria are being used to assess and compare competing antigens, and delivery systems to focus resources on to the most credible vaccine candidates. Emphasis and resources are being focused on moving candidate vaccines into clinical trials.

EXPECTED AND OBTAINED RESULTS

EMVDA anticipates the development of a vaccine to reduce the burden of malaria.

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PRIBOMAL

PRECLINICAL STUDIES TOWARDS AN AFFORDABLE, SAFE AND EFFICACIOUS TWO-COMPONENT PAEDIATRIC MALARIA VACCINE

Acronym:	PRIBOMAL
Project number:	LSHP-CT-2006-037494
EC contribution:	€ 2 345 358
Duration:	36 months
Type:	STREP
Starting date:	1 January 2006
Project website:	www.crucell.com

BACKGROUND

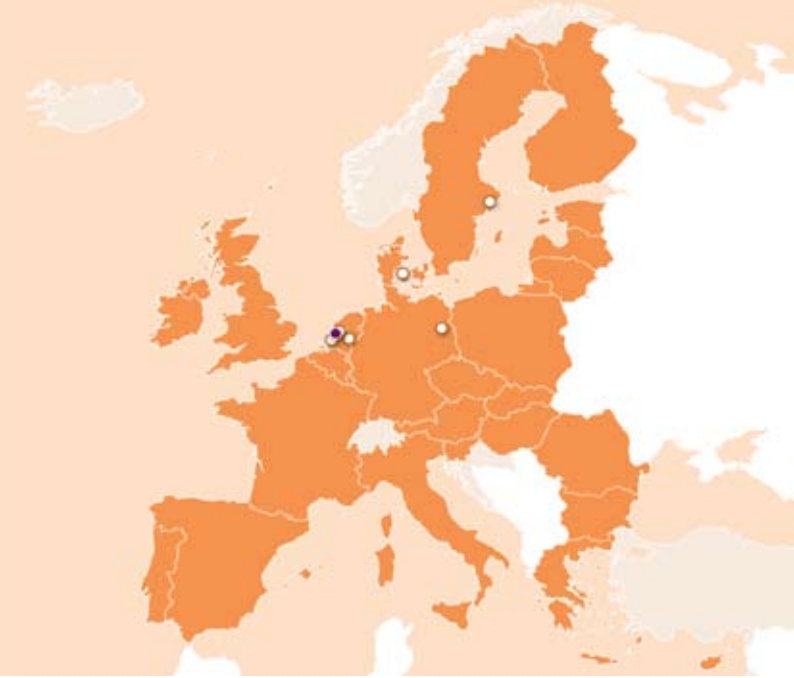
About 1 to 2 million people die of malaria every year, mostly in sub-Saharan Africa. Predominant among the victims are pregnant women and children. Nearly 90% of these child malaria deaths are in children younger than 5 years. A safe, affordable paediatric malaria vaccine that provides long lasting protection against malaria urgently needs to be designed. This project is generating and testing an innovative malaria vaccine consisting of a prime, to be administered at birth, of a novel recombinant Bacille Calmette-Guérin (BCG) vector carrying preferentially multiple antigens derived from the Plasmodium falciparum parasite - the cause of malaria. The priming vaccine will be followed by a booster vaccination 14 weeks after birth.

AIMS

The consortium aims to show in preclinical studies the safety and efficacy of a novel and affordable two-component paediatric malaria vaccine.

EXPECTED AND OBTAINED RESULTS

The project will deliver an effective paediatric malaria vaccine candidate ready for development and clinical trials. Extensive knowledge will be gained regarding immunological features of different vaccination schedules, in combination with information on their protective ability. This information will help design future malaria vaccines.



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SME-MALARIA

SME LED MALARIA VACCINE INITIATIVE

Acronym:	SME-Malaria
Project number:	LSHP-CT-2006-018918
EC contribution:	€ 1 700 000
Duration:	36 months
Type:	STREP
Starting date:	1 March 2006
Project website:	www.malariastrep.eu

BACKGROUND

The attenuated MeV vaccine on which this project's vectors are based is used worldwide, with excellent safety and efficacy records. As the vaccine is easy to produce economically, the vector is of great interest for the development of multivalent vaccines for poor countries, such as in sub-Saharan Africa. The genetics of MeV and the technology for rescue of recombinant MeVs is well established and the long-lasting immunogenicity induced both in transgenic mice susceptible to MeV infection and in macaques using several vectored transgenes up to 5 kb in length, has been documented.

The most promising P. falciparum antigen-vector combinations will be used in monkey immunisation studies (these animals can be efficiently infected with MeV) to determine various aspects of potential safety, as well as humoral and cellular immunity.

This project is investigating new malaria vaccine candidates with the objective of taking at least one through to Good Laboratory Practices (GLP) pilot scale up. The most promising candidates will undergo *in vitro* and *in vivo* testing, lead optimisation, and safety and toxicology testing according to GLP standards.

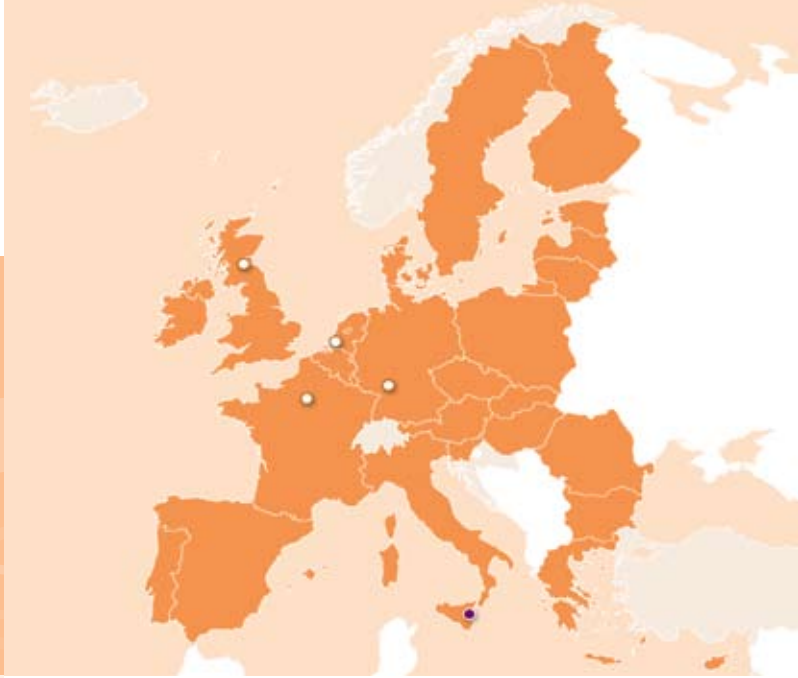
The two selected antigens, MSP-1 and AMA-1, are leading vaccine candidates associated with the surface of merozoite, the parasite form that invades uninfected erythrocytes. Both were originally identified as targets of antibody-based immunity directed against asexual blood stage parasite multiplication. It has subsequently become clear that both antigens are also expressed during the development of liver stage schizonts (the prelude to blood stage development). They represent potential targets for cellular immunity-based mechanisms of immunity and protection.

AIMS

The project aims to obtain at least one malaria vaccine candidate stably expressed in MeV that induces humoral and cellular immune responses.

EXPECTED AND OBTAINED RESULTS

SME-Malaria expects that at least one of the candidate antigens will prove efficacious and safe following preclinical studies; it will then be produced under GLP conditions.



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MALINV

DIFFERENTIAL EXPRESSION OF MALARIA INVASION-ASSOCIATED PROTEINS IN THE POROZOITE: NOVEL VACCINATION STRATEGY

Acronym:	MALINV
Project number:	LSHP-CT-2004-012199
EC contribution:	€ 587 000
Duration:	24 months
Type:	STREP
Starting date:	1 June 2005
Project website:	www.cochin.inserm.fr/

BACKGROUND

In humans, sterile immunity against malaria was only obtained after exposure to irradiated sporozoites inoculated by mosquitoes. Recently, antigens by invasion blood stage parasites have been shown to be expressed by sporozoites, which leads to the hypothesis that they might also be involved in sporozoite invasion of hepatocytes.

The three antigens investigated to date may not be responsible for induction of optimal protective responses. This would account for the difficulties encountered in reproducing this sterile long-lasting immunity by current sub-unit vaccines. It would clearly be desirable to investigate other pre-erythrocytic antigens.

AIMS

The project's aims were:

a. to list all potential genes within the ebl and rh families in *P. falciparum, P.*
b. *berghei* and *P. yoelii*. Real-time polymerase chain reaction (RT-PCR) was performed for each gene on ribonucleic acid (RNA) purified from all the stages of these parasites, and the expression profile in sporozoites determined;
c. to obtain recombinant proteins, peptides and immunological reagents specific to each gene product expressed in sporozoites;
d. to characterise the proteins expressed in the sporozoite using reagents obtained in item 2, above;
e. to obtain transgenic parasite lines in which sporozoite-expressed genes identified in item 1 are individually disrupted or knocked out, and to purify the corresponding sporozoites;
f. to employ the reagents from item 2, to determine the functional role of each protein in sporozoite invasion;
g. to employ the sporozoites obtained in item 4, to assess the functional role of each protein during the lifecycle;
h. to employ the reagents from item 2 and item 4, to conduct immunisation studies;
i. to conduct a detailed analysis of immune responses resulting from item 7, and derive surrogate markers of protection.

EXPECTED AND OBTAINED RESULTS

MALINV characterised the new invasion-associated sporozoite antigens from three species of *Plasmodium* and assessed their role in hepatocyte invasion, to develop immunogens for vaccination studies and assess their efficacy against a sporozoite challenge.

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TB-VAC

AN INTEGRATED PROJECT FOR NEW VACCINES AGAINST TUBERCULOSIS

Acronym:	TB-VAC
Project number:	LSHP-CT-2004-503367
EC contribution:	€ 17 000 000
Duration:	60 months
Type:	Article 169
Starting date:	1 January 2004
Project website:	www.tb-vac.org

BACKGROUND

Tuberculosis (TB) causes about two million deaths a year, with around 98% occurring in developing countries. Within these countries, the HIV pandemic has had a major impact on TB, resulting in an additional one million deaths per year. With the rise in drug-resistant strains of TB, the disease may once again become a major threat to Europe. No effective vaccine is available yet.

In recent years, several promising new vaccine strategies have been developed. This project aimed to integrate European efforts towards the development of novel tuberculosis vaccine candidates and forward these vaccines to small-scale phase 1 human clinical trials in Europe and Africa. Under the coordination of the Animal Sciences Group in Lelystad, Netherlands, the project joined 33 leading European institutions from nine European and four African countries, including two major vaccine producers.

AIMS

The main aims of the project are:
the discovery and development of new tuberculosis vaccine candidates effective in the young adult population;

- the development of tests that predict vaccine efficacy in humans;
- the clinical evaluation of lead candidates in small initial trials in Europe and Africa;
- capacity building in developing countries for clinical evaluation of vaccines;
- liaising with other consortia to coordinate specific activities;
- liaising with the European and Developing Countries Clinical Trials Partnership (EDCTP) to enable further large clinical trials in Africa.

EXPECTED AND OBTAINED RESULTS

TB-VAC expects to deliver the following results via two tracks:

Track 1: Optimisation of existing vaccine candidates towards phase I trials:

- Strategic development:

- Optimised production of new and selected vaccines by combining the best delivery system/adjuvant available with the best antigen or antigens known.
- Definition of robust correlates of protective immunity against M. tuberculosis and surrogate markers of TB disease for monitoring and developing effective TB vaccines.
- Evaluation of the efficacy of various selected vaccine candidates and their associated responses to mycobacteria and various mycobacterial components.

These results should allow the selection of a second generation of improved vaccines for clinical assessments in the downstream development component.

- Downstream development:

- Production in Europe of promising candidate vaccines according to international quality requirements for production.
- Establishment of a complete pre-clinical file to satisfy national and European regulatory authorities.
- Establishment of vertical product development teams for the most promising candidate-vaccines to ensure full communication and continued professional efforts from the upstream vaccine development down to clinical trials
- Phase 1 clinical trials designed and conducted in three European centres in areas of low TB endemicity and, later, in three centres of excellence in endemic areas in Africa.

The results of these studies allowed the selection of vaccines that could be further clinically developed in phase 2 trials (for example via the EDCTP).

Track 2: New vaccines/antigen discovery:

- Optimisation of live vaccines previously identified with an efficacy better than BCG.
- Discovery of new immuno-modulatory ligands for improved vaccine efficacy.
- New candidate sub-unit antigens with a major focus given to dormancy/latency-associated antigens, the latter group being of particular interest.
- Selected vaccine antigens (those with efficacies as good as BCG) will be optimised (particularly by combining selected antigens) and evaluated for efficacy in Track 1.

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NEOTIM

INNATE AND ADAPTIVE IMMUNITY IN CLINICAL AND EXPERIMENTAL MYCOBACTERIAL INFECTION IN NEONATES AND INFANTS

Acronym:	Neotim
Project number:	LSHP-CT-2005-018736
EC contribution:	€ 2 000 000
Duration:	36 months
Type:	STREP
Starting date:	1 November 2005
Project website:	www.euprojekt.su.se/index.php/kb_1/io_1307/io.html

BACKGROUND

It is estimated that over two million people worldwide die each year from tuberculosis (TB), a major infectious disease that most commonly attacks the lungs. Most frequently TB is a disease that affects adults, but the proportion of paediatric TB is expanding. Due to its chronic nature, the disease is still prevalent in childhood, including the neonatal period. A significantly increased pool of knowledge is required in regards to the immune protection of neonates and children against Mycobacterium tuberculosis. New insight may allow for combined targeting of innate and adaptive immune systems – highly relevant in the rational design of vaccines.

AIMS

The Neotim project aims to compare neonates/infants and adults in terms of protective responses generated during mycobacterial infections or vaccination with novel mycobacterial antigens in murine experimental systems and in humanised mice (reconstituted with human lymphoid and myeloid cellular populations). The following activities are being conducted:

- comparing innate and adaptive immune responses, with an emphasis on dendritic cells and T-cells;
- investigating neonatal and adult mice during mycobacterial infection and following inoculation of a novel and promising candidate vaccine, methylated HBHA;
- investigating such responses using mice reconstituted *de novo* with human lymphoid and myeloid hemopoietic-derived cell lineages (allowing, for the first time, an experimental dissection of human immunity to mycobacteria); monitoring and comparing the immune responses of naturally infected humans in the corresponding age groups;
- investigating the human molecular basis of hyper-susceptibility to live BCG in rare neonates with disseminated BCG disease in order to discover novel mycobacterial susceptibility genes, which will then be tested in the humanised mouse model.

EXPECTED AND OBTAINED RESULTS

The Neotim consortium expects the results to provide a conclusive assessment of the role and regulation of the neonatal/infant immune system in determining the outcome of mycobacterial infections. The data obtained during the project will also determine whether the use of selected mycobacterial antigens, together with innate immunomodulatory molecules, will offer significant protection against human tuberculosis.

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VACCINES4TB

GENOME - AND HLA-WIDE SCANNING AND VALIDATION OF CYTOTOXIC CD8 T CELL RESPONSES AGAINST MYCOBACTERIUM TUBERCULOSIS

Acronym:	Vaccines4TB
Project number:	LSHP-CT-2004-012175
EC contribution:	€ 1 053 445
Duration:	24 months
Type:	STREP
Starting date:	1 January 2005
Project website:	www.biocompetence.eu/index.php/kb_1/io_3555/io.html

BACKGROUND

Each year, 54 million people are infected with Mycobacterium (M.) tuberculosis, 6.8 million develop clinical disease, and 2.4 million people die of tuberculosis (TB). Among infectious diseases, TB is responsible for the greatest number of deaths (five percent of all deaths worldwide). As such, vaccinations against TB are urgently required.

A growing body of evidence from animal studies indicates that CD8 T cells are involved in the control of latent M. tuberculosis infection. However, relatively little has been published on the functional role of mycobacteria-specific CD8 T cells in humans, nor on the actual mycobacterial antigens and epitopes targeted by these killer cells.

AIMS

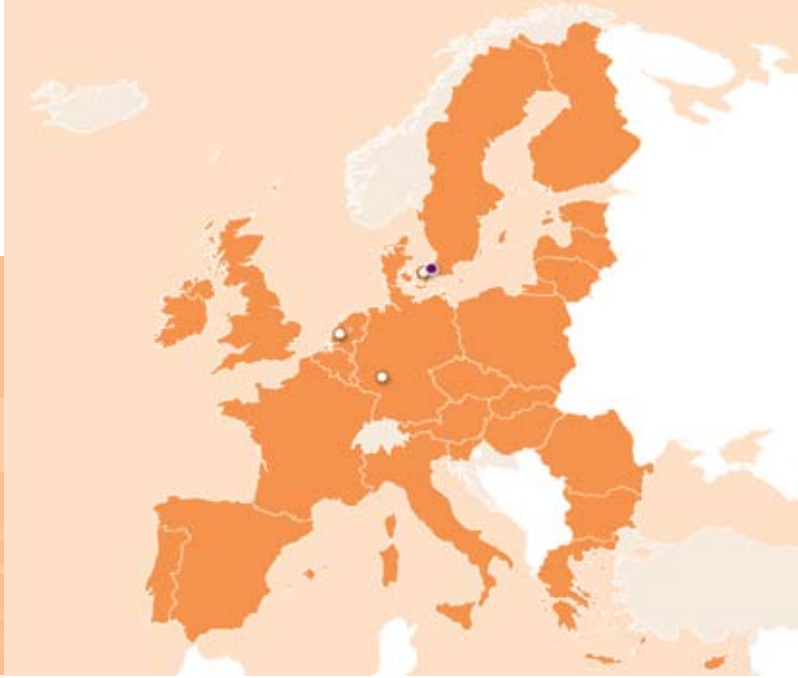
The specific aims of the project were to:

- evaluate the CD8 cytotoxic T cell (CTL) response repertoire in the human population;
- test if expression libraries representing the whole M. tuberculosis genome can be used for CTL antigen discovery;
- test that the use of immuno-bioinformatics is a fast and rational approach to CTL epitope identification.

EXPECTED AND OBTAINED RESULTS

The project expected to find new CTL epitopes. More specifically, it anticipated:

- identifying proteins likely to be good antigens, using expression cloning of M. tuberculosis antigens and M. tuberculosis–derived epitopes seen by patient CTLs;
- predicting which peptides are potential CTL epitopes within all M. tuberculosis proteins for all major human HLA supertypes, and select a fraction of these for actual synthesis and test;
- measuring binding to HLA molecules for the predicted peptides;
- measuring CTL responses against predicted epitopes in M. tuberculosis infected persons and BCG vaccinated individuals using either: (1) target cells transfected with the M. tuberculosis expression library and relevant HLA molecules or (2) target cells pulsed with identified peptides.



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IMMUNOVACTB

A NEW APPROACH FOR DEVELOPING A LESS IMMUNOSUPPRESSIVE VACCINE FOR TUBERCULOSIS

Acronym:	ImmunoVacTB
Project number:	LSHP-CT-2006-037388
EC contribution:	€ 857 298
Duration:	24 months
Type:	STREP
Starting date:	June 2007

BACKGROUND

Infections due to Mycobacterium tuberculosis cause over two million deaths each year. A major problem in combating tuberculosis is the insufficient efficacy of the current vaccine, M. bovis BCG. This is due to the fact that BCG induces the Th2 cytokine IL-4 and the immunosuppressive cytokine IL-10, apart from the protective Th1 cytokines Il-12 and IFNγ. Current data suggest that two mycobacterial glycolipids — lipoarabinomannan (LAM) and phenolic glycolipid (PGL) — play an important role in this immunosuppression.

AIMS

The project aims to find a new strategy to overcome these known problems of inefficacy, and will design less immunosuppressive BCG strains, lacking PGL and/or (parts of) the mannose cap. Immuno VacTB will isolate BCG strains that lack the LAM mannose cap (or parts thereof). This will be done in BCG with an intact as well as with an interrupted pks15/1 gene. These recombinant single or double mutant BCG strains will be evaluated *in vitro* and *in vivo* for their ability to induce cytokine production and to protect against tuberculosis in a murine infection model.

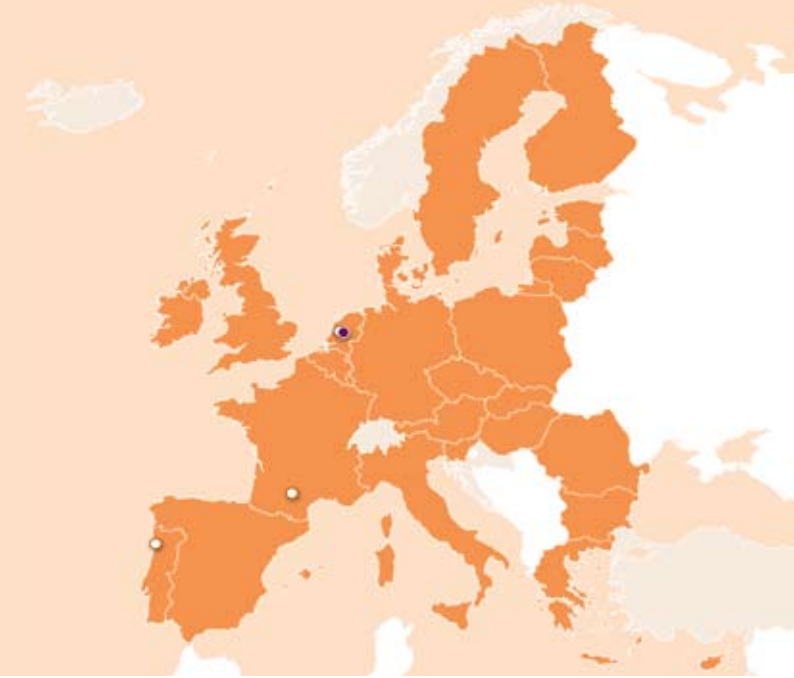
The project will construct novel BCG strains that lack (part of) the mannose cap of lipoarabinomanan and/or cannot produce phenolic glycolipid. These strains will be an interesting platform from which to introduce M. tuberculosis genes encoding important antigens, or non-mycobacterial genes that enhance an immunoprotective response.

EXPECTED AND OBTAINED RESULTS

The following results are expected:

- construction of BCG mutants that cannot synthesise (part of) the mannose cap of LAM and/or PGL;
- determination of the structure of LAM and PGL in the mutants;
- determination of the effects of the mutations on cytokine production by human DCs and T cells as well as murine macrophages *in vitro* (the same experiments will be performed with purified LAM);
- determination of the effect of the mutations on protection against murine tuberculosis *in vivo*.
- It is hoped that new and improved insights will also be gained into how the immune system is manipulated by mycobacterial glycolipids, with the aim of developing an improved M. bovis BCG vaccine.

As of april 2008: the capless LAM mutant, the PGL mutant and the double mutant have been constructed in BCG. The in vivo testing of these strains by the Porto group is under way.



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FLUVACC

LIVE ATTENUATED REPLICATION-DEFECTIVE INFLUENZA VACCINE

Acronym:	FLUVACC
Project number:	LSHB-CT-2005-518281
EC contribution:	€ 9 200 000
Duration:	60 months
Type:	IP
Starting date:	1 September 2005
Project website:	www.greenhillsbiotech.com/eu_projects.html

BACKGROUND

Industrial production of influenza vaccine still relies on traditional techniques. Essentially, chicken eggs are used as mini vaccine factories. They are injected with live influenza virus, and incubated for several days so that the virus can multiply. The egg is then opened, and the virus is harvested, purified and inactivated. Unfortunately, highly pathogenic avian viruses do not grow well in eggs as they tend to kill the embryo. There are many other problems associated with egg-based production. Since the whole process is time-intensive and hard to scale up, it may be difficult for supply to meet demand during a pandemic. In addition, the combination of vaccine with egg proteins can lead to allergic reactions in some people. FLUVACC aims to shift vaccine production away from the traditional methods, with the generation of live attenuated-replication deficient vaccines that can be produced in cell culture. Instead of using egg-produced viral proteins, the live attenuated vaccines developed by the FLUVACC consortium contain whole replication deficient viruses that generate a strong immune response, but that are non-pathogenic.

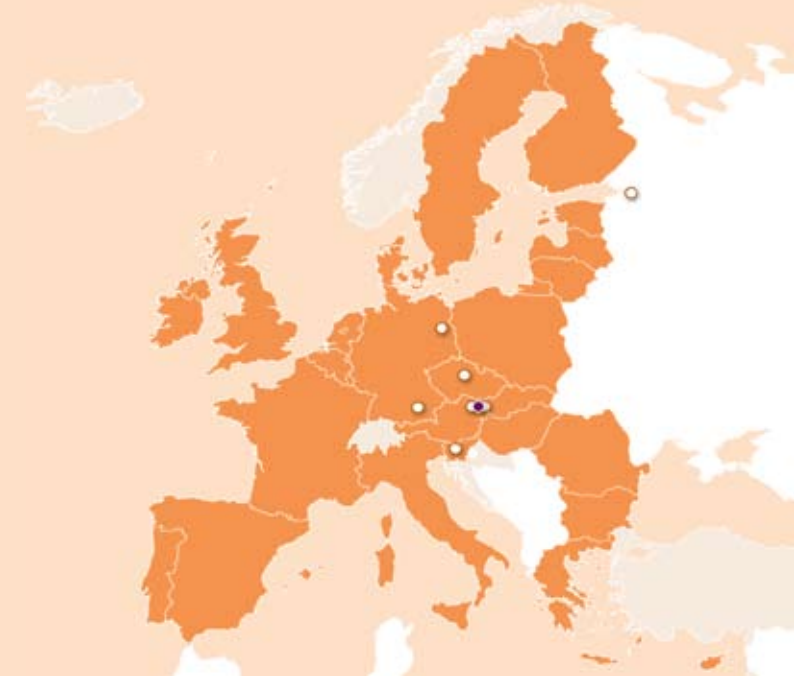
AIMS

The aim of this project is to develop a novel vaccine against influenza. This vaccine is a novel component of European systemic efforts to prevent and control influenza, based on a replication deficient virus that is generated by a specialised technique known as reverse genetics. The vaccine will be produced in cell culture.

Another important aim is to improve core technology for live attenuated vaccine production, using a technique called reverse genetics. The project has developed a “master strain” that is lacking the NS1 gene which is essential for productive viral replication. Candidate vaccines for emerging influenza subtypes can be quickly produced by inserting their genes into this master strain so that they express the immunogenic surface proteins, but remain replication-deficient. This master strain was adapted to grow to high titers in tissue culture, making it possible to produce large quantities in the case of a pandemic.

EXPECTED AND OBTAINED RESULTS

The FLUVACC vaccine will contribute to the efforts to prevent and control influenza. The proposed vaccine will reduce mortality and morbidity rates, lost workdays and hospitalisations.



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FLUVAC

DOSE SPARING AND INCREASED IMMUNOGENICITY FOR VACCINATION AGAINST PANDEMIC INFLUENZA WITH COVACCINE HT

Acronym:	FluVac
Project number:	LSHB-CT-2007-044407
EC contribution:	€ 3 500 000
Duration:	48 months
Type:	STREP
Starting date:	1 October 2007
Project website:	www.fluvac-project.eu.

BACKGROUND

The risk of a new influenza pandemic is emphasised by a WHO report documenting several hundred recent cases of human infection with a new virus strain and an approximately 50 % mortality rate. On a global scale, the impact of an influenza pandemic can be enormous, and a pandemic outbreak could have serious social and economic consequences on human life, as well as place a large burden on healthcare systems. High costs of anti-influenza drugs and their limited availability has revealed an urgent need for an affordable vaccine for the prevention and control of an outbreak.

AIMS

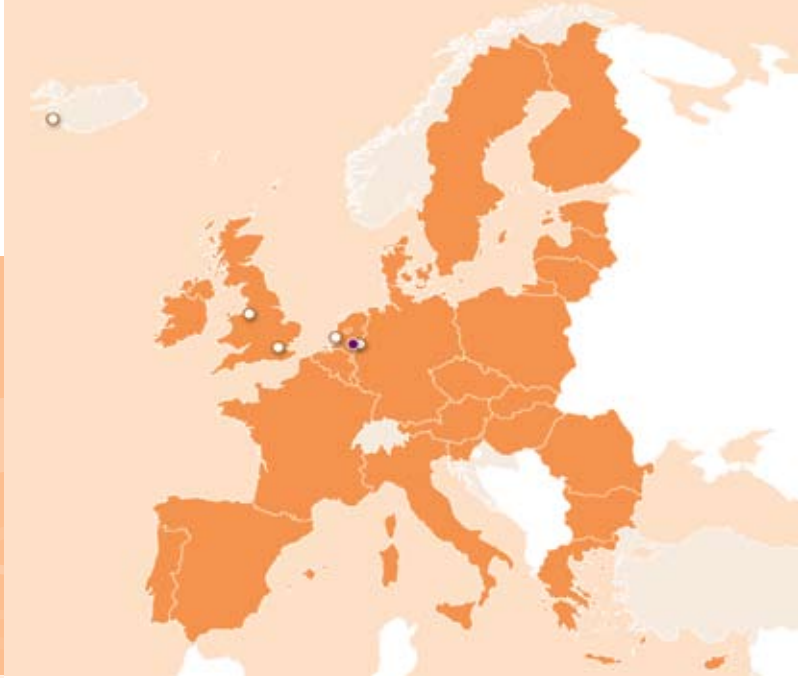
This project is aiming at a novel influenza vaccine formulation by combining CoVaccine HT and H5N1. Feasibility studies with the adjuvant have indicated that CoVaccine HT is a promising candidate for emergency vaccines to establish high levels of immunity and to compensate for the limited availability of antigen. The ultimate goal is to prove the safety and efficacy of a CoVaccine HT adjuvanted pandemic whole H5N1 virus vaccine in humans, and to gain insight in its performance in animal models.

Another objective is to exploit cell culture technology for antigen production, as this method is more flexible, independent of supply of animal-derived materials and more consistent.

It will also target the delivery of a prototype emergency vaccine to control or prevent a pandemic. In preclinical and clinical studies, the project will test optimal doses of inactivated, cell culture-derived whole influenza virus (H5N1) and CoVaccine HT as adjuvant. The novel adjuvant CoVaccine HT has been shown to elicit high humoral and cellular responses against different types of antigens (including the inactivated influenza virus) in different animal species. It is considered to be a promising candidate for a pandemic influenza vaccine.

EXPECTED AND OBTAINED RESULTS

The FluVac project and subsequent development and registration of the vaccine will have great benefits for the health of the European population. It will also contribute to the development of a novel generation of adjuvants and of improved vaccines to combat infectious diseases.



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PANFLUVAC

EFFICACIOUS VACCINE FORMULATION SYSTEM FOR PROPHYLACTIC CONTROL OF INFLUENZA PANDEMICS

Acronym:	PANFLUVAC
Project number:	LSHB-CT-2007-044115
EC contribution:	€ 3 334 798
Duration:	48 months
Type:	STREP
Starting date:	1 January 2007
Project website:	www.panfluvac.org

BACKGROUND

Influenza epidemics remain a burden for both human health and national economies, as witnessed by the recent advance of the pathogenic avian H5N1 influenza virus. For a truly efficacious vaccine, one must consider the route of virus entry into the host (the respiratory tract), and host requirements for protective immune defences. While parenterally-administered inactivated influenza vaccine is the best prophylactic control measure, parenteral vaccination does not ensure induction of local immunity in the respiratory tract — the route by which the virus infects humans — and from where it transmits to other individuals. Inducing mucosal immunity by vaccination would enhance control of both disease and transmission.

AIMS

PANFLUVAC aims to produce an efficacious vaccine formulation to meet immediate and future needs for controlling influenza epidemics and pandemics. The project is constructing vaccine delivery systems for intranasal and parenteral vaccines. New H5N1 vaccines are to be based on well-established virosome technology - which has proven its worth for efficacious interpandemic vaccines - as well as whole virus vaccines. This will permit a comparison of the intranasal virosomal vaccine with the whole virus vaccine.

EXPECTED AND OBTAINED RESULTS

The expected results are:

- a formulated H5N1 pandemic vaccine developed from existing technologies and
- for preclinical evaluation;
- virosomal and whole virion vaccines (existing technologies) compared in preclinical
- evaluations;
- evaluated intranasal and parenteral administration;
- a pandemic influenza vaccine to meet the current need for required vaccines in the face of
- imminent pandemic influenza threat;
- the efficacy of the formulated H5N1 pandemic vaccine generated from existing technologies assessed by phase I clinical trial evaluation;
- studies in vaccinated subjects in order to generate a knowledge platform on immunological correlates and correlates of protection challenged;
- an erudite link formulated, joining preclinical and clinical evaluations;
- a dossier prepared on proposed H5N1 vaccines formulated with novel adjuvants.

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INTRANASAL H5VACCINE

PROTECTIVE EFFICACY OF INTRANASAL DEL NS1 (H5N1) INFLUENZA VACCINE

Acronym:	Intranasal H5vaccine
Project number:	P5B-CT-2007-044512
EC contribution:	€ 2 680 400
Duration:	36 months
Type:	STREP
Starting date:	1 January 2007
Project website:	www.greenhillsbiotech.com/eu_projects.html

BACKGROUND

Avian influenza is now posing a threat to mankind. Between 2003 and 2006 the WHO reported 161 cases of avian influenza A of the H5N1 strain in humans; of these 86 were fatal. At the moment is not clear how the virus is transferring to humans. Old human influenza viruses of the H1N1 or H2N2 subtypes could also return in humans and sooner or later there will almost certainly be an influenza pandemic unless new and more efficient vaccines are developed.

AIMS

The Intranasal H5vaccine project is developing a novel vaccine against avian influenza. It is assessing immunological properties; conducting preclinical experiments and establishing novel, sensitive methods for the assessment of the antibody response against viral proteins. These assays will allow for the selection of an optimal vaccine candidate that will be subsequently evaluated in clinical trials.

The project will also test the protective properties of the vaccine against homologous and heterologous influenza strains in ferret challenge experiments, using different H5 strains. In order to close the gap between the ferret model and human studies, the project will use the macaque model to evaluate the immune response. These preclinical studies will allow the selection of the most potent vaccine candidate, which will be produced according to cGMP (current Good Manufacturing Practice) guidelines on Vero cells. After a toxicological evaluation of the vaccine, clinical phase I/II studies will be performed. A human challenge study using the attenuated H5 virus will be carried out, if permitted by the authorities. Alternatively, for proof of principle of the del NS technology, an H1-del NS1 vaccine will be produced and used in an H1 challenge study.

EXPECTED AND OBTAINED RESULTS

The project aims to define an intranasal H5N1 pandemic vaccine with enhanced capacity to elicit a strong, long-lasting local and systemic immune response in humans.

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CHIMERIC VACCINES

DEL NS1 VIRUS AS A VECTOR FOR FOREIGN ANTIGENS

Acronym:	CHIMERIC VACCINES
Project number:	COOP-CT-2004-512864
EC contribution:	€ 1 384 945
Duration:	30 months
Type:	SMEs – Cooperative Research Project
Starting date:	1 November 2004
Project website:	www.greenhillsbiotech.com/eu_projects.html

BACKGROUND

Influenza viruses are species-specific and only rarely cross the species barrier. Of the hundreds of strains of avian influenza A viruses, only four are known to have caused human infections: H5N1, H7N3, H7N7 and H9N2. These mostly cause mild symptoms, but the exception is the highly pathogenic H5N1 virus, which has crossed the species barrier to infect humans in recent years, leading to the outbreak of avian influenza that began in December 2003. A novel vaccine needs to be developed to provide protection against avian and seasonal influenza.

AIMS

This project developed a novel approach for a vaccine. The technology was based on the insertion of selected epitopes into a genetically modified influenza virus that is apathogenic. To achieve these results, the project identified both a stable vector and promising antigens. Antigen selection was based on bioinformatics methods that were substantiated by experimental validation. The properties of the backbone vector in terms of safety and stability were assessed in preclinical experiments and gave highly satisfactory results. To bring the proposed chimeric vaccine into clinical trials, a production process in small scale was established, using a novel purification technology.

EXPECTED AND OBTAINED RESULTS

Results of this project have shed light on important aspects in the development of novel vaccination strategies and will help to further develop the concept of a chimeric vaccine. In addition, important information regarding immunogenicity and safety is being generated, and a process for the production of purified viruses established.

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UNIVERSAL VACCINE

NOVEL ANTIGEN -ADJUVANT VEHICLE AS AN EFFECTIVE INFLUENZA VACCINE

Acronym:	Universal Vaccine
Project number:	COOP-CT-2005-017749
EC contribution:	€ 1 154 717
Duration:	24 months
Type:	SMEs – Cooperative Research Project
Starting date:	1 June 2005
Project website:	www.universalvaccine.org

BACKGROUND

One of the biggest problems in trying to develop reliable influenza vaccines is that flu viruses tend to mutate frequently. Influenza vaccines work by stimulating the body's immunity against the haemagglutinin and neuraminidase proteins on the virus's surface. But there is a third protein - M2 - that until now has not been the focus of much attention. The extracellular domain of this protein, M2e, has been remarkably conserved in the amino acid sequence since the human influenza virus was first isolated in 1933. Scientists are focusing on this protein as a possible breakthrough for a universal vaccine. If it could stimulate an adequate immune response, it might be possible to develop a broadspectrum vaccine against all influenza A subtypes. Previous research has shown that when the extracellular domain of M2 (M2e) is linked to appropriate carrier particles, such as the hepatitis B virus core, it becomes highly immunogenic.

AIMS

The project aimed to:

- utilise the M2e peptide as antigenic determinant;
- develop a powerful, new, safe and easily-administered nasal vaccine for humans that provides lifelong protection against influenza;
- covalently fuse the M2e-peptide with the CTA1-DD adjuvant, creating a strongly immunogenic influenza vaccine suitable for mucosal delivery;
- further improve vaccine efficacy by incorporating the fusion protein in proprietary liposomes;
- increase the *in vivo* maintenance of the antigen by using blocked or constrained peptides or peptidomimetics;
- determine the *in vivo* mechanism of action of the mucosal influenza vaccine;
- demonstrate the safety and efficacy of the vaccine in animal challenge models.

EXPECTED AND OBTAINED RESULTS

The expected result was the development of an efficacious, innovative, safe and easily-administered nasal vaccine for humans that provides lifelong protection against influenza.

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HEPACIVAC

NEW PREVENTATIVE AND THERAPEUTIC HEPATITIS C VACCINES: FROM PRECLINICAL TO PHASE I

Acronym:	HEPACIVAC
Project number:	LSHB-CT-2007-037435
EC contribution:	€ 8 800 000
Duration:	60 months
Type:	IP
Starting date:	1 January 2007
Project website:	www.altaweb.eu/hepacivac

BACKGROUND

Liver disease caused by the hepatitis C virus (HCV) infection affects an estimated 123 million people worldwide. No vaccine is available and the best antiviral therapy, a combination of interferon alpha and ribavirin, is only effective in a minority of patients. A growing body of data suggests that virus-specific T cell responses are associated with clearance of HCV in acutely infected humans and chimpanzees.

The first vaccine candidate is gene based, encodes for the 2 000 amino acid-long HCV Non Structural region (from NS3 to NS5B) and utilises adenoviral vectors for delivery. These vectors have been shown to elicit potent CD4+ and CD8+ T cell responses in rodents and primates. Recently, a proof-of-concept vaccination and heterologous challenge experiment in chimpanzees showed that potent, broad and long-lived T cell responses to HCV were elicited in vaccinated animals. The gene-based vaccine protected against acute and chronic disease, induced by a challenge with a high dose of a heterologous HCV strain. The second vaccine candidate consisted of recombinant HCV glycoproteins, gpE1 and gpE2, which were associated to resemble a pre-virion envelope structure.

Protection against homologous and heterologous challenge, mediated by CD4+ T cell response and antibodies, was observed in experiments with chimpanzees. The findings showed that both vaccine candidates have the potential to protect humans from a large number of viral strains. The complementary action of these vaccines might be extremely instrumental in making a vaccine against HCV, which is able to stimulate several components of the immune system and to elicit efficacious immune responses, both in preventative and therapeutic vaccination settings.

AIMS

The long-term objective of the HCV vaccine programme is to develop both prophylactic and therapeutic vaccines that elicit antiviral CD4+ and CD8+ responses, capable of doing one of the following:

- reducing the rate of incidence and/or persistence of HCV infection following exposure (for a prophylactic vaccine);
- increasing the rate of clearance of HCV infection as a monotherapy, and/or in combination with current therapy or novel antiviral therapy (for a therapeutic vaccine).

EXPECTED AND OBTAINED RESULTS

The HEPACIVAC project will provide the opportunity to analyse immune correlates of protection from HCV infection in detail, as well as to standardise immunogenicity assays and to establish benchmark references for future preclinical and clinical studies of HCV candidate vaccines.

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DISSECT

DEVELOPMENT OF INTERVENTION STRATEGIES AGAINST SARS IN A EUROPEAN-CHINESE TASKFORCE

Acronym:	DISSECT
Project number:	SP22-CT-2004-511060
EC contribution:	€ 2 375 892
Duration:	36 months
Type:	STREP
Starting date:	1 October 2004
Project website:	www.cnb.uam.es/~webcoron/EUprojectdissect/

BACKGROUND

Severe Acute Respiratory Syndrome (SARS) was initially detected in Guangdong province, China. It has been proven that the etiological agent of SARS is a new coronavirus (CoV) with the acronym SARS-CoV.

The recent outbreak constitutes an important challenge to the capabilities of EU Member States, and confirms that new communicable disease outbreaks require a specific focus. Actions should attempt to address longer term research commitments, define appropriate sustainable priorities and encourage collaboration with partners from SARS-affected areas in third countries. There is an urgent need to develop strategies for preventive therapy for healthcare workers, who could eventually be vaccinated, and then for other target groups who should be vaccinated.

The emergence of SARS has created serious economic and societal problems in China, reducing human and commercial interaction. The project created a European-Chinese task force to combat SARS, and create essential links between two parts of the world.

AIMS

This project encompasses all the complementary aspects necessary for the development of intervention strategies, including *vaccination, immunotherapy, and antivirals* to protect against SARS. In addition, techniques and materials will be generated to develop *diagnostic kits* that will lead to the identification of infected individuals at very early steps of the disease, and to differentiate between vaccinated and naturally infected people. The *first focus of the project is vaccine development*. Accordingly, a set of complementary strategies is proposed to guarantee the success. These strategies include "classical" vaccines (such as whole *inactivated virus*), *subunit vaccines*, and state of the art-*recombinant technology derived vaccines*. The second focus of the project is on the state of the art-*therapeutic approaches*, ranging from the use of monoclonal antibodies to specific antivirals. For achieving the primary objectives of this project, the availability of an adequate preclinical setting for SARS-CoV research, including *animal models*, as well as the access to relevant clinical samples are absolute preconditions. These all met in this project, as a result of the expertise of the individual groups involved. To develop this comprehensive project, laboratories from the European Union and China are collaborating. The laboratories from EU member states (Spain, UK and The Netherlands) have a long-term experience (more than twenty years) in coronavirus pathology, immunology and molecular biology. The groups from China have key knowledge on the onset and evolution of SARS, high technology, and have generated large collections of biological materials: viruses, sera, tissues, clinical and epidemiological data.

EXPECTED AND OBTAINED RESULTS

A. PRODUCTION OF SARS-CoV ANTIGENS IN DIFFERENT EXPRESSION SYSTEMS. Significant progress has been done on the expression of viral proteins (including S, S1, S2, M, E, N, 3a, 6, and 7a) in different systems (bacteria, mammalian cells, baculoviruses, yeast and plants). Several SARS-CoV antigens providing protection against SARS-CoV have been produced in different expression systems.

B. PRODUCTION OF A RECOMBINANT VACCINE FOR SARS-CoV. The construction of a recombinant vaccine for SARS-CoV has been one of the most successful outcomes of the project. The efficacy of this vaccine has been shown in two animal model systems, hamsters and transgenic mice.

C. A SARS-CoV replicon that is self-amplified with high efficiency has been constructed. This replicon will be very useful to screen anti-virals without the need to use infectious virus.

D. Development of an inactivated SARS-CoV vaccine. The attenuated rSARS-CoV engineered is an excellent starting point for the production of a chemically inactivated vaccine. This development has important practical

applications, as inactivated vaccines are safer and could be applied immediately in the event of a reemergence of SARS-CoV

E. Role of accessory 3a, 6 and 8 proteins in virus host interaction. Following the discovery and characterization of 3a protein O-glycosylation, which was meanwhile published, it was established that this protein interacts with the viral M protein, though this interaction is weak. The evolution and processing of ORF 8 has been studied. Protein 6 has been involved in replication.

F. DEVELOPMENT OF ANIMAL MODEL SYSTEMS TO EVALUATE PROTECTION AGAINST SARS. Both ferret and macaque have been developed as animal models for SARS-CoV, and these models have been refined and characterized.

G. DEVELOPMENT OF SARS-CoV DIAGNOSTIC SYSTEMS. An APEX microarray system to diagnose respiratory viruses, including SARS-CoV has been developed.

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SARSVAC

IMMUNOPREVENTION AND IMMUNOTHERAPY OF SARS INFECTION

Acronym:	SARSVAC
Project number:	SP22-CT-2004-511065
EC contribution:	€ 1 200 000
Duration:	36 months
Type:	STREP
Starting date:	1 March 2004
Project website:	www.novartis.it

BACKGROUND

The SARS (Severe Acute Respiratory Syndrome) epidemic of 2003 swept across 30 countries, affected a reported 8 422 people, 916 of whom died, and almost completely paralysed Asia's economy. Aggressive quarantine measures and rising summer temperatures successfully terminated the first eruption of SARS, allowing doctors and scientists to consolidate what they learned about the disease and plan for possible future outbreaks.

This project was prepared in response to urgent medical and societal needs for immunopreventive (vaccination) and immunotherapeutic measures for SARS. An integrated strategy for developing effective vaccines and for establishing effective therapeutic treatment was developed. The strategy for vaccine development followed two parallel approaches: i) the preparation of a classical inactivated vaccine (as already done for other coronaviruses), ii) the definition of potential antigens and T/B protective epitopes through the study of SARS-CoV derived virus-like particles (VLP), pivotal to the understanding of SARS-CoV morphogenesis and virion maturation. The immunotherapeutic strategy relied on development and validation of neutralising human antibodies to SARS-CoV. Under this project, academia experts in immunology, vaccinology, and molecular biology joined forces with industrial vaccine production experts, in order to develop preventive and therapeutic measures for SARS.

AIMS

The project aimed to produce an efficacious vaccine formulation to meet immediate and future needs for protection against SARS infections as well as immunotherapeutic measures for SARS.

EXPECTED AND OBTAINED RESULTS

In 2004, project partners filed for patent protection for an innovative killed-virus vaccine that can protect against SARS coronavirus infections. Commercial availability is expected in 2014. The project also succeeded in developing human monoclonal antibodies against SARS CoV, which can be utilised for passive immunotherapy. Antibody material has been stored, suitable for animal and structural studies. Furthermore, project partners collaborated with the US-based NIH for the development of a recombinant vaccine based on SARS virus-like particles (VLP) which are non-infectious but can stimulate the production of antibodies and immune T-cells.

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SARS/FLU VACCINE

DEVELOPMENT OF A COMBINED INFLUENZA/ SARS VACCINE

Acronym:	SARS/FLU VACCINE
Project number:	LSHB-CT-2004-512054
EC contribution:	€ 1 607 500
Duration:	36 months
Type:	STREP
Starting date:	1 January 2005
Project website:	www.greenhillsbiotech.com/eu_projects.html

BACKGROUND

In 2002, an atypical pneumonia, characterised by progressive respiratory failure, emerged in southern China. The causative agent was rapidly identified as a new coronavirus – designated as Severe Acute Respiratory Syndrome-associated virus SARS-CoV. The disease swept rapidly to neighbouring regions and led to several international cases, including Canada. By the end of the epidemic, in July 2003, about 8 000 SARS cases and almost 800 deaths due to SARS were recorded worldwide. Since then, the world is in an inter-epidemic period, as no new cases have been reported.

AIMS

The aim of the project was to test constructs for immunogenicity. The ones that provoke the best immune response without compromising safety in animal testing will be selected for a full preclinical testing programme.

EXPECTED AND OBTAINED RESULTS

It is hoped that the project will result in a SARS/flu vaccine that has the potential to induce protective immune responses against SARS-CoV and the influenza virus with one immunisation.

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NOVADUCK

NOVEL AI DIVA RECOMBINANT VACCINES FOR DUCK

Acronym:	NOVADUCK
Project number:	SSPE-CT-2006-044217
EC contribution:	€ 1 416 380
Duration:	36 months
Type:	STREP
Starting date:	1 January 2007
Project website:	www.novaduck.eu

BACKGROUND

The ongoing outbreak of highly pathogenic avian influenza (HPAI) caused by the H5N1 virus has caused widespread concern as H5N1 can occasionally cross the species barrier to infect humans. Ducks play a major role in the epidemiology of avian influenza (AI) because wild waterfowl, including ducks, constitute the natural reservoir of all subtypes of influenza A virus. Experimental infection of ducks with recent isolates indicates a longer shedding period and a selection for lower virulence variant, suggesting that duck has become the "Trojan horse" of Asian H5N1 Avian Influenza (AI) (Hulse-Post et al., 2005).

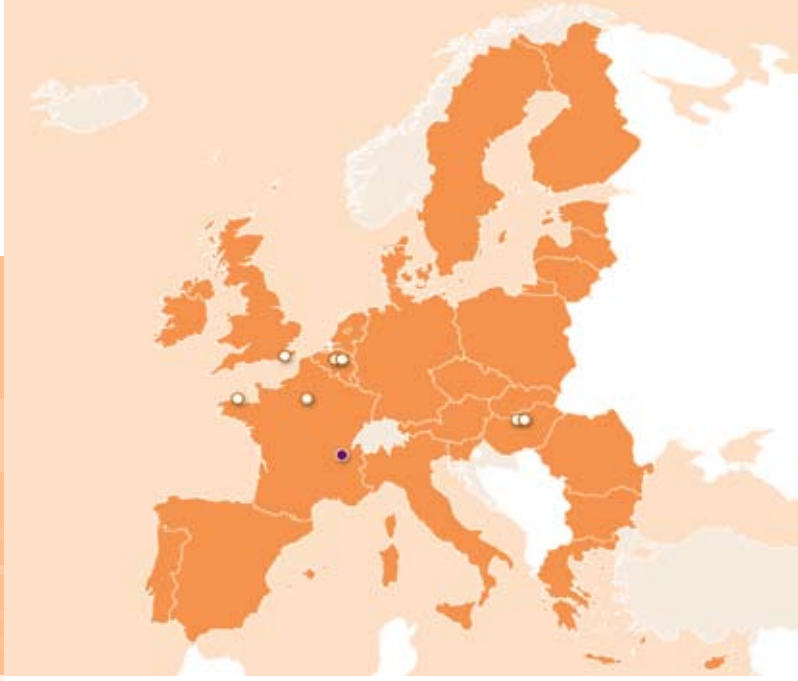
Although biosecurity is the first line of defence against HPAI, strategic use of vaccination is clearly recognised as a tool to help eradicate HPAI in an infected country. Most studies evaluating the efficacy of AI vaccines have been performed in chickens; duck studies have been relatively rare. Existing inactivated AI vaccines are less immunogenic in ducks than in chickens and must generally be administered twice to be fully efficient. At present there is no commercially available DIVA test to monitor AI infection in birds injected with this type of vaccine. Therefore, highly efficient, cost-effective, DIVA-compatible AI vaccines for ducks are still greatly needed. In this specific context, live vector-based vaccines hold the greatest promise and are one of the most effective options. Indeed, some live recombinant vector-based AI vaccines have shown excellent results in chickens, but they are not necessarily adapted for use in ducks. Expected advantages of this type of vaccine include administration at a younger age, mass administration, rapid onset of immunity, and compatibility with the DIVA strategy.

The NOVADUCK project is designed to demonstrate and exploit the potential of live vector vaccines to develop a new generation of highly efficient and cost-effective AI vaccines for ducks and therefore could contribute to reduce AI from the ecosystem.

AIMS

The NOVADUCK project aims to develop and evaluate new highly protective and cost-effective avian influenza live vaccines for ducks based on live vectors and in line with the DIVA strategy. More specifically, it is:

- identifying the optimal AI immunogenic sequence (s) to be inserted into the selected live vectors;
- generating and optimising three types of live recombinant vector-based vaccines;
- developing reliable and cost-effective duck-specific immunological tools to measure the immune response induced by the different vaccine candidates and to detect infection in a vaccinated duck (DIVA strategy);
- assessing the safety and immunogenicity of the new vectored vaccine candidates and comparing it with those of existing vaccines to select the best vaccine candidate(s);
- setting up a challenge model in ducks for vaccine evaluation of efficacy;
- measuring the efficacy of the most immunogenic vectored vaccine candidates against recent HPAI H5N1 and comparing it with existing vaccines;
- studying the effect of vaccination on genetic/ antigenic drift;
- selecting the best candidate(s) to be developed based on its (their) immunogenic and protective properties as well as its (their) estimated cost of production and administration mode flexibility (e.g. individual versus mass administration).



EXPECTED AND OBTAINED RESULTS

The project is expected to obtain the following results:

- Identification of the best viral vector vaccine for ducks; the immunogenicity of three poxvirus-based vectors was studied; a second type of vector has been developed and will be soon assessed in ducks; the development of a third vector is ongoing;
- identification of the optimal AI immunogenic sequence to be inserted into a vector; a first DNA vaccination study performed in ducks allowed the selection of a highly immunogenic AI gene ; a new study will compare the immunogenicity of additional AI genes including a gene mix allowing the generation of retrovirus-based virus-like particles;
- development of new tools to evaluate the duck immune response; reagents and techniques are currently being developed to evaluate the humoral, cellular and mucosal immune response induced by AI vector vaccines in ducks; in particular, DIVA tests and their compatibility with these vector-based vaccines are being evaluated;
- development of a reproducible AI challenge model in ducks for vector vaccine efficacy studies;
- definition of the minimal level of protection that should be expected for an acceptable AI duck vaccine standard for evaluation of efficacy of duck AI vaccine;
- production of data on the effect of vaccination of ducks on genetic/antigenic drift of the challenge virus;

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AIV VACC DIAGNOSIS

VACCINE, DIAGNOSTIC TEST DEVELOPMENT AND IMMUNOLOGY ASPECTS OF AVIAN NFLUENZA

Acronym:	AIV VACC DIAGNOSIS
Project number:	SSPE-CT-2007-044141
EC contribution:	€ 1 372 890
Duration:	36 months
Type:	SSA
Starting date:	1 December 2006
Project website:	www.aiv-vacc-diagnosis.com

BACKGROUND

The highly pathogenic H5N1 avian influenza currently circulating in Asia, and recently in northern and western Africa and Europe, has led to the deaths of more than 150 million birds and 150 humans. Due to the seriousness of this threat some countries are taking steps to vaccinate their entire poultry population. Currently a consensus is emerging that vaccination of birds at risk could be a critical part of a control strategy in averting a human pandemic.

Although very useful in the fight against avian influenza, all currently available influenza vaccines have considerable shortcomings. Several vaccines developed over the past two decades to protect poultry against the highly pathogenic H5 or H7 are based on inactivated whole virus vaccines. Apart from the challenge of setting up a robust diagnostic test for differentiating vaccinated from infected animals, these vaccines have to be administered by labour intensive and expensive parenteral injections.

AIMS

The primary aim of this project is to develop better avian influenza vaccines through live or vector vaccines that could be mass applicable through spray, drinking water or eye drops. These vector vaccines would offer considerable advantages - mass applicable, less labour intensive and animal friendly application, protection by local and systemic immunity and less interference with eventual maternal antibodies, more complete protection through cellular and humoral immunity, faster onset of immunity when used in face of an outbreak and cheaper production methods.

EXPECTED AND OBTAINED RESULTS

This project is expected to deliver the first mass applicable live vaccine against highly pathogenic H5N1 avian influenza. The vaccine would offer major technical advantages, including production aspects, over the currently existing vaccines.

The development of molecular biological tools will allow in the future a quicker response to changes in antigenicity of the field-virus. The construction of gene cassettes that will allow fast integration of the H region of future genetically and antigenically different influenza strains in the ND vector will allow a much faster response for construction of updated vaccine strains.

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SCOOTT

SUSTAINABLE CONTROL OF ONCHOCERCIASIS TODAY AND TOMORROW

Acronym: SCOOTT
Project number: INCO-CT-2006-032321
EC contribution: € 2.8 million
Duration: 48 months
Type: STREP
Starting date: 10 November 2006

BACKGROUND

Onchocerciasis (river blindness) is caused by the filarial nematode *Onchocerca volvulus*, which is transmitted through the bite of blackflies. Currently it afflicts 37 million people, 95% of whom live in West and Central Africa. Control relies on mass treatment with ivermectin. However, this neither kills adult worms nor permanently stops microfilarial production. Furthermore, there is emerging resistance, and in areas where loiasis (*Loa loa*) is also endemic ivermectin cannot be used for mass treatment because of the risk of allergic reactions. An alternative may be tetracyclines whose activity is directed against *Wolbachia*, an endosymbiont bacteria that has been discovered in *Onchocerca* spp. *L loa* does not possess *Wolbachia*, so tetracyclines would provide a safe therapy in loiasis-endemic areas.

Experiments performed with the *O. ochnegi* cattle model and *Litomosoides sigmodontis* mouse models have demonstrated the feasibility of vaccination against filarial parasites. These models, with the human studies, have identified the key effector mechanism of protective immunity. Work is now focused on identification of the protective [vaccine] antigens.

AIMS

The aims of the project are to improve sustainable control of onchocerciasis through:

- refinement of existing chemotherapeutic regimes by use of doxycycline to complement ivermectin treatment and further screening of existing drugs;
- assessment of immunological sequelae of ivermectin intervention and their implications for improved control strategies;
- identification of new targets, including vaccine candidates, and approaches for integrated control.

EXPECTED AND OBTAINED RESULTS

It is hoped that the project will:

- establish processes for effective community-directed treatment of onchocerciasis with doxycycline;
- determine efficacy and feasibility of using doxycycline for treatment of onchocerciasis;

determine the impact of ivermectin and doxycycline treatment on immune responses of humans and in two animal models (*O ochengi* in cattle and *Litomosoides sigmodontis* in mice);

identify mechanisms of protective immunity in two animal models (*O ochengi* in cattle and *Litomosoides sigmodontis* in mice);

- assess the impact of drug treatment on protective immune responses in the two animal models;
- identify vaccine antigen candidates.

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TRANCHI

T CELL REGULATION AND THE CONTROL OF HELMINTH INFECTIONS

Acronym:	TRANCHI
Project number:	INCO-CT-2006-32436
EC contribution:	€ 1 950 000
Duration:	36 months
Type:	STREP
Starting date:	1 October 2006
Project website:	http://tranchi.org

BACKGROUND

Helminth infections are among the most neglected communicable diseases afflicting developing countries. Pharmacological treatments are compromised by rapid re-infection, variable compliance and emerging resistance. Vaccination has not yet succeeded in evoking strong resistance. The critical question in helminth control remains why the immune system fails to clear parasites, which may be due to the presence of a newly-identified cell type, the Regulatory T cells (Treg).

AIMS

The project will establish whether Regulatory T cells, lymphocytes with immunosuppressive properties, are active in chronic helminth infections, and if so, whether targeting such cells may offer an immunological cure to the major tropical diseases of filariasis and schistosomiasis. It will achieve these by carrying out the following:

- profiling the type and functions of Tregs in filariasis and schistosomiasis infected humans;
- comparing Treg activity in patient groups of differing infection status/levels of pathology;
- establishing if polymorphisms for regulatory genes are linked to Treg profiles in humans;
- demonstrating the role of Tregs in helminth-associated hyporesponsiveness;
- testing whether neutralisation of Tregs restores immune responsiveness in human cells;
- testing whether neutralisation of Tregs restores immunity to infection in animal models;
- characterising human Treg gene expression and T cell receptor usage;
- assessing community and health system issues for new immunological interventions.

EXPECTED AND OBTAINED RESULTS

The project's results are expected to include:
a database containing all clinical and parasitological data required.

- an understanding of the relationship between Treg activity and infection status, intensity and pathology in filariasis and schistosomiasis.
- testing the hypothesis that Tregs maintain helminth infection in animal model systems.
- a mini-gene array for expression analysis of genes associated specifically with Tregs.
- simple, accurate and high throughput genotyping that is user friendly.
- molecular gene expression profile of Treg cells.
- TCR usage and antigen specificity of Treg cells.
- a comprehensive analysis of the extent and patterns of polymorphisms in regulatory genes in Indian, Indonesian and African populations.
- appraisal of perceptions and attitudes towards new immunological interventions.

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BOVAC

DEVELOPMENT OF A PROPHYLACTIC VACCINE AND DIAGNOSTIC MARKERS TO DIAGNOSE AND PREVENT LYME BORRELIOSIS SPECIFIC TO EUROPE AND NORTH AMERICA

Acronym:	BOVAC
Project number:	COOP-CT-2004-512598
EC contribution:	€ 1 355 443
Duration:	30 months
Type:	STREP
Starting date:	16 September 2004
Project website:	www.bovac.org

BACKGROUND

Lyme disease or borreliosis (LB) is the commonest tick-borne disease in Europe. It can be transmitted to humans when they are bitten by ticks carrying species of the Borrelia bacterium. Infection is often diagnosed by a rash (Erythema migrans) that spreads out from the site of the tick bite. If caught early, the disease can be prevented with oral antibiotics. However, if left untreated, the bacteria can spread through the bloodstream, access various tissues and cause severe diseases including meningitis, arthritis and carditis. Official incidence rates in Europe range from 0.3 to 150 cases per year per 100 000 population. However, few countries have made LB a notifiable disease, so these rates are only an approximation. Many experts believe that actual rates of LB infection could be up to seven times higher.

No vaccine exists for the European version of the disease, despite the fact that in some countries the disease has had a significant socioeconomic impact. Innovative technology was applied in this project by several jEuropean SMEs and universities, to identify and isolate antigens common to all Borrelia species causing borreliosis. The project used state-of-the-art molecular biology techniques, namely the ANTIGENome technology, to identify and isolate prospective antigens.

AIMS

The aim of the project was to select novel vaccine candidates suitable to develop a vaccine to prevent LB. The consortium was also interested in using the identified antigens to evaluate their use in developing novel diagnostic tools for LB as well as assessing the importance of LB in Austria and the Czech Republic by a thorough epidemiology study.

EXPECTED AND OBTAINED RESULTS

The key objective of the project was the development of vaccine candidates effective against LB. The consortium identified more than 100 novel antigens using the ANTIGENome technology and identified first candidates in an animal model of LB infection. Furthermore, the epidemiologic studies revealed novel insights into the infestation of ticks by LB and other pathogens on a country-wide level. The obtained results build a strong basis for the further development of an LB vaccine.

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SAVINMUCOPATH

NOVEL THERAPEUTIC AND PROPHYLACTIC STRATEGIES TO CONTROL MUCOSAL INFECTIONS BY SOUTH AMERICAN BACTERIAL STRAINS

Acronym:	SAVINMUCOPATH
Project number:	INCO-CT-2006-032296
EC contribution:	€ 1 699 908
Duration:	36
Type:	STREP
Starting date:	1 October 2006
Project website:	www.greenhillsbiotech.com/eu_projects.html

BACKGROUND

Enteric and respiratory diseases cause many thousands of deaths worldwide. Bacteria that invade the enteric and respiratory mucosa are the focus of this project and in particular *Streptococcus pneumoniae, Salmonella enteritidis* and *Bordetella pertussis* which are associated with serious rates of morbidity and mortality, especially in young children and low socio-economic status people. These infectious strains are unique to Latin America and the scientific community has neglected development of specific therapies and vaccines.

AIMS

The main aims of the project are to gain understanding of the host-pathogen interaction and to develop novel mucosa-specific therapeutics and vaccines to control bacterial infections. Innate defences are up-regulated at mucosal sites upon detection of conserved microbial molecules and contribute both to the immediate barrier function to mucosal colonisation and the long lived antigen-specific mucosal immune responses. These molecules thus have early immunostimulatory activities and adjuvant properties on mucosa. The project's strategy is to take advantage of these natural mechanisms to improve clearance and immunoprophylaxis against the selected life-threatening pathogens.

Bacterial strains are being studied in experimental animal mucosal infection models in order to (i) characterise the innate mechanisms of early elimination of pathogens and the concomitant mechanisms of induction of mucosal adaptive immunity, (ii) define the proof of concept that conserved microbial molecules can activate mucosal immunity, and (iii) identify novel mucosa-specific pathogen molecules with biological activities on mucosal innate and adaptive immunity using purified bacterial components and screening on cell and animal models.

EXPECTED AND OBTAINED RESULTS

The expected result is identification of molecules from the selected bacteria that activate specifically protective mucosal innate immunity to block the infections at the port of entry of bacteria and stimulate antigen-specific responses through mucosa. The project also hopes to define the signature of innate protection against the selected pathogens.

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OMVAC

NOVEL PREVENTION AND TREATMENT POSSIBILITIES FOR OTITIS MEDIA THROUGH THE COMPREHENSIVE IDENTIFICATION OF ANTIGENIC PROTEINS

Acronym: OMVac
Project number: LHSB-CT-2006-037653
EC contribution: € 2 320 000
Duration: 36 months
Type: STREP
Starting date: 1 October 2006

BACKGROUND

Otitis Media (OM) is one of the most prevalent childhood diseases and the most common reason for the prescription of antibiotics. Approximately 80% of all children experience an episode of acute OM by three years of age. Recurrent OM affects up to 40% of children and may persist for periods of weeks to months, causing symptoms ranging from hearing loss and tinnitus to anorexia or conjunctivitis. The main causative agents are the bacterial pathogens *Streptococcus pneumoniae, Haemophilus influenzae* (NTHi) and *Moraxella catarrhalis*, which colonise the middle ear, often after a primary viral infection. Considering the high direct and indirect costs of OM, there is an urgent need for an alternative and effective therapy.

AIMS

The main objective of this project is the identification of novel vaccine candidates from NTHi and *M. catarrhalis* to develop a prophylactic vaccine against OM. Bacterial surface display libraries will be constructed and screened with human sera from exposed individuals to define the ANTIGENome of both pathogens. Following thorough *in vitro* validation selected antigens will be evaluated in experimental animal models of OM.

The project is also addressing the comprehensive characterisation of natural immune responses against proteineacous antigens of the major three bacterial pathogens causing OM. Moreover, the function of protective antigens during pathogenesis and biofilm formation will be investigated.

EXPECTED AND OBTAINED RESULTS

The project expects the following results:

- comprehensive identification of antigens from *M. catarrhalis and* NTHi, by using Intercell's ANTIGENome technology and complementary proteomic approaches;
- *in vitro* and *in vivo* validation of identified antigens to select the most promising vaccine candidates;
- characterisation of protective antigens with respect to their role in pathogenesis of *M. catarrhalis* and NTHi (including biofilm formation);
- definition of natural immune responses against the identified antigens from *M. catarrhalis*, NTHi and *S. pneumoniae*, using the available sera and Ig preparations.

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HEVAR

HERPESVIRUS-BASED VACCINES AGAINST ROTAVIRUS INFECTIONS

Acronym:	HEVAR
Project number:	INCO-CT-2006-032209
EC contribution:	€ 1 540 000
Duration:	36 months
Type:	STREP
Starting date:	1 December 2006

BACKGROUND

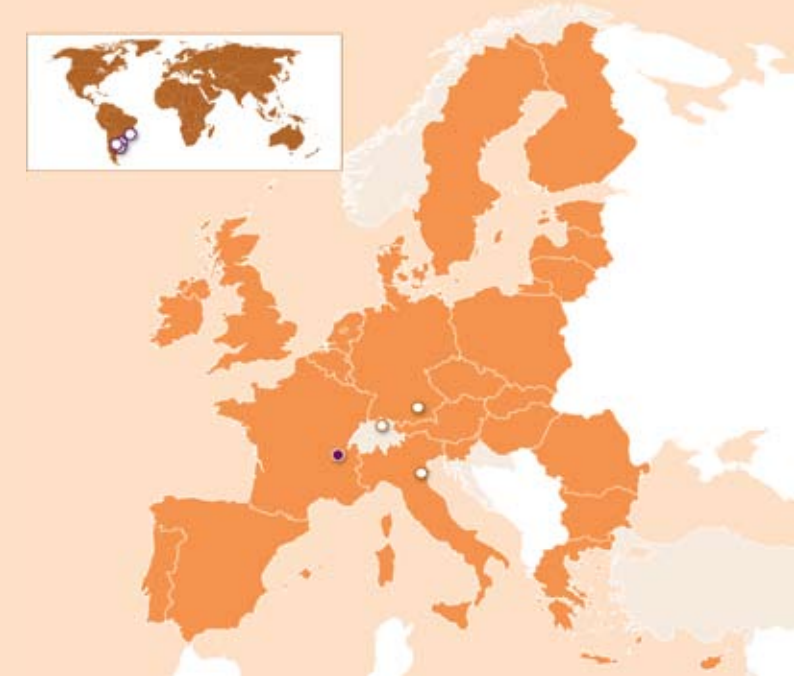
Diarrhoea caused approximately two million deaths per year worldwide in the last decade and was responsible for an estimated 20% of mortality in children aged less than four years in developing countries. Rotaviruses are the most common cause of severe dehydrating diarrhoea in young children in these countries, accounting for 20% to 60% of hospitalised cases. Rotavirus infection and disease cannot be controlled by hygiene and sanitation measures. There is an urgent need for the development and deployment of an effective prophylactic anti-rotavirus vaccine that would have universal application as part of childhood immunisation programmes.

AIMS

The project's aim is to contribute to a better understanding of the immune biology of rotavirus infections using a novel generation of gene transfer vectors, as a first step towards the development of innovative genetic vaccines to fight against these pathogens. To this end, HEVAR will develop herpes simplex virus type 1 (HSV-1)-based vectors for the generation and analysis of rotavirus-specific expression and display model vaccines. This approach is based on the possibility of engineering HSV-1-based vectors expressing and/or displaying rotavirus antigens, either individually or in combination, alone or together with immune-modulator genes.

EXPECTED AND OBTAINED RESULTS

The main deliverables of HEVAR will be a set of toolboxes containing a large collection of HSV-1-based and DNA-based vectors expressing mouse rotavirus antigens that will be already evaluated in mice. These toolboxes will also contain a set of vectors expressing human rotavirus antigens from strains with epidemiological significance in South America. All these tools will be accessible to any academic team wishing to use them for vaccine development or research on rotaviruses. Knowledge of the complex technologies required to locally generate, produce and evaluate the HSV-1-based gene transfer vectors will therefore be transferred from European groups to South American partners.



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SUPASALVAC

SALMONELLA-FREE BROILERS BY LIVE VACCINE-INDUCED INNATE RESISTANCE TO COLONISATION AND INVASION AND NOVEL METHODS TO ELIMINATE VACCINE AND FIELD STRAINS

Acronym:	SUPASALVAC
Project number:	FOOD-CT-2004-505523
EC contribution:	€ 2 400 000
Duration:	42 months
Type:	STREP
Starting date:	1 February 2004

BACKGROUND

The European poultry industry urgently needs a cost-effective way of dealing with salmonella in broilers (young chickens) in order to produce quality-assured, pathogen-free meat at a competitive price. The immune system of broilers is insufficiently developed when they are slaughtered (before six weeks) and, as a consequence, they frequently succumb to infection by pathogenic salmonella. Strategies are required for the biological control of the food borne infection in broilers, including further investigation of promising 'designer' vaccines for newly hatched chicks.

AIMS

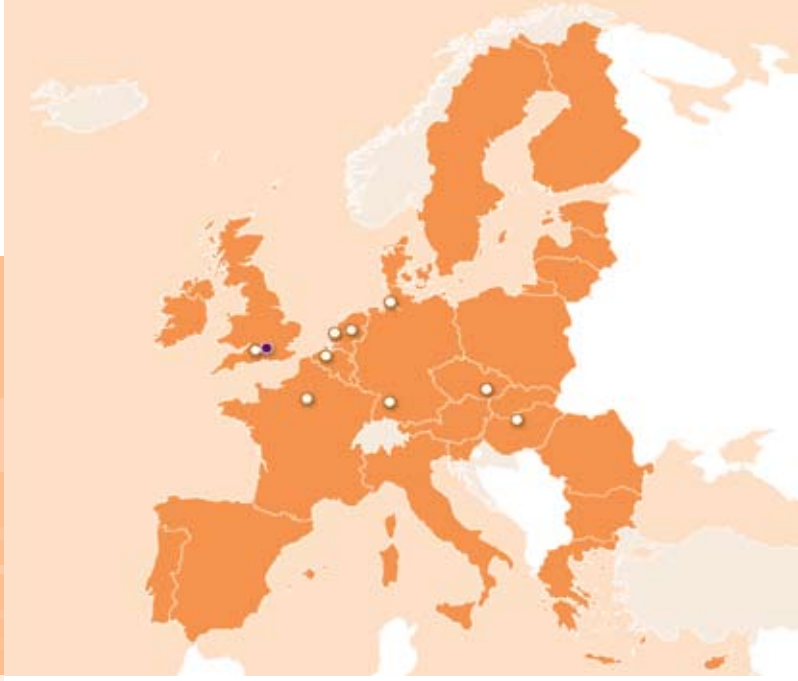
This project aims to use biotechnology to enhance the effects of live salmonella vaccines. The activities include the following:

- testing strains of salmonella to see which are best at inhibiting colonisation by similar strains;
- discovering which genes are involved in inhibition;
- identifying the genes that draw chick immune cells to the gut in response to the live vaccine;
- identifying the role of intestinal defensin peptides in controlling colonisation.

The project will also investigate other methods of preventing colonisation of chick intestines by salmonella, exploring dietary additives or methods of inhibiting bacterial genes active during colonisation. Furthermore, bacteria-killing viruses (known as bacteriophages) will be used to target particular bacteria. The project is developing phages to destroy salmonella, both in broilers and in carcasses.

EXPECTED AND OBTAINED RESULTS

The results of the SUPASALVAC are expected to pave the way to producing a highly effective live vaccine designed for young chicks (based on the best inhibiting strains) with the genes to promote chick immunity.



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TRYPADVAC2

DEVELOPMENT OF AN "ANTI-DISEASE" VACCINE AND DIAGNOSTIC TESTS FOR AFRICAN TRYPANOSOMOSIS

Acronym:	TRYPADVAC2
Project number:	INCO-CT-2005-003716
EC contribution:	€ 900 000
Duration:	36 months
Type:	STREP
Starting date:	1 June 2005
Project website:	www.trypadvac2.eventos.usb.ve/

BACKGROUND

Trypanosomosis, or African sleeping sickness, is a disease that affects both humans and livestock. Today nearly a third of Africa is affected by Trypanosomosis which is caused by a parasite transmitted by the bite of the tsetse fly. The disease is having a detrimental effect on the development of African rural communities as it restricts the keeping of farm animals which affects supplies of meat and milk and also limits the development of mixed arable and livestock farming.

Previous studies of trypanosome infections have focused on congopain, an immunosuppressive cysteine protease (CP) of Trypanosoma congolense. As the effects of immunisation with congopain are limited, association with other antigens is required.

Recent developments in the field of proteomics and progress in the genome mapping of trypanosomes have provided tools for the study of new pathogenic pathways. In order to improve diagnosis of the disease, procedures for antibody detection will be developed and/or validated. They are based on recombinant technology, which circumvent problems associated with the current use of parasite extracts. Recombinant and synthetic peptides from CPs and heat shock proteins, both previously identified as major antigens, as well as newly described molecules, will be assessed for their diagnostic potential. Techniques for detection of parasite antigens in the host tissues will be re-examined using recently developed monoclonal antibodies.

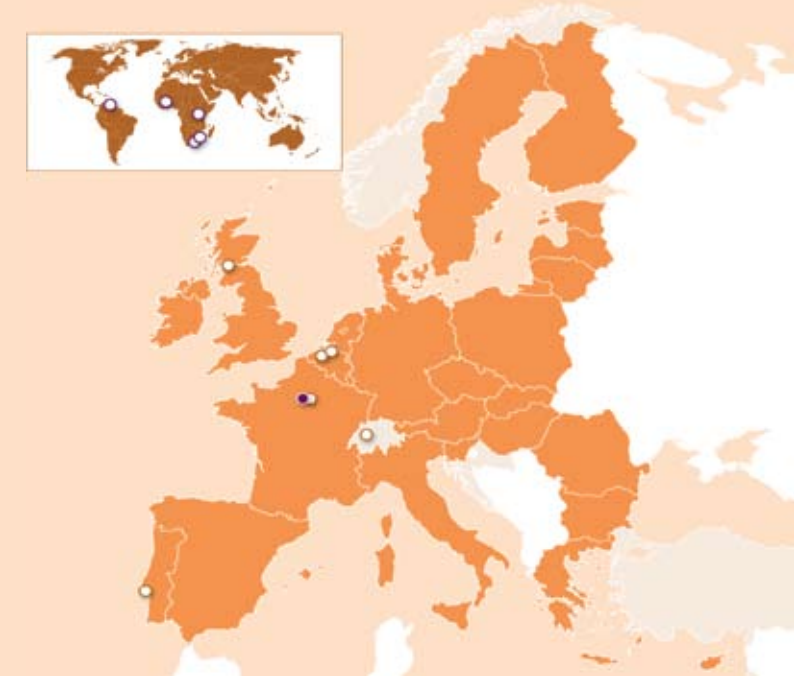
AIMS

The aim of the project is to contribute to the eradication of Trypanosomosis in humans and livestock through limitation of trypanosome-associated pathology and accurate diagnostics of trypanosome infections. It is also proposed to develop immunisation strategies against pathogenic factors of trypanosomes.

The current proposals will include screening and characterisation of other pathogenic molecules, especially those responsible for anaemia. A number of other trypanosome proteases - CPs, serine and metallo-proteases - require characterisation as to their biological roles in the parasite and the host. Trypanosomes also contain protease inhibitors, some of which have immunomodulatory effects. They may thus be manipulated, directly or in association with their partner enzymes, to modulate the disease.

EXPECTED AND OBTAINED RESULTS

The expected result is a vaccine against Trypanosomosis.



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CANCERIMMUNOTHERAPY

CANCER IMMUNOLOGY AND IMMUNOTHERAPY

Acronym: CANCERIMMUNOTHERAPY
Project number: LSHC-CT-2006-518234
EC contribution: € 12 185 102
Duration: 48 months
Type: IP
Starting date: 1 March 2006
Project website: www.cancerimmunotherapy.eu/

BACKGROUND

Cancer is a major life-threatening disease and the second greatest cause of mortality in Europe after cardiovascular 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 progression to metastatic disease. In addition, these approaches are very toxic in themselves, 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.

AIMS

The first part of the project consists of vaccination clinical trials for the comparison of various vaccines, such as peptides and RNA, with different types of immunological adjuvants and dendritic cells. Safety and clinical efficacy are the primary endpoints of these trials. A huge effort is being made to monitor the anti-vaccine T cell responses, as examining the correlation between immunological and clinical responses to the vaccines is crucial to understanding which factor(s) limit tumour regression. A second part of the project, tightly connected to the clinical trials since it uses biological material from the vaccinated patients, consists of optimising tumour vaccines and combating immune evasion.

Prospective 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 the project partners to design improved vaccines. Finally, considering the complexity of mechanisms that may lead to or prevent tumour regression in vaccinated patients, the project proposes exploring 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.

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 the partners are investigating, will also have a greater clinical efficacy.

The project will build a close interaction between the research laboratory and the clinic, as this will allow new ideas to emerge from observations made in either of these two fields, and to be rapidly integrated into new projects.

EXPECTED AND OBTAINED RESULTS

The project hopes to develop a therapeutic cancer vaccine with defined tumour antigens that will provide a clinical benefit in at least 40% of patients. This 40% threshold 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.

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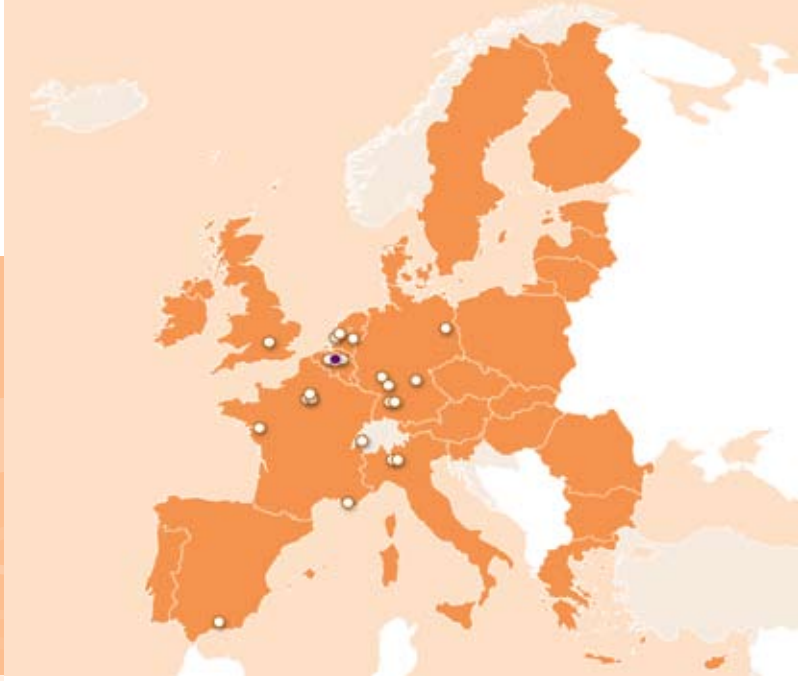

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DENDRITOPHAGES

THERAPEUTIC CANCER VACCINES

Acronym:	DENDRITOPHAGES
Project number:	LSHP-CT-2003-503583
EC contribution:	€ 1 999 900
Duration:	36 months
Type:	STREP
Starting date:	1 April 2004
Project website:	www.idm-biotech.com/

BACKGROUND

The ultimate goal of anticancer therapeutic vaccines is to prevent metastasis development and tumour progression, as well as to provide long-term protection. Previous studies have shown no side effects associated with this type of dendritic autologous cellular drug, and immune and clinical responses were achieved in some patients who were resistant to conventional therapies.

AIMS

The project aimed to demonstrate the immune and clinical efficacy, reproducibility and feasibility of anticancer cell vaccine by sequential steps: (i) the best dendritic cell (DC) vaccination strategy via preclinical studies was selected; (ii) the immune response was monitored in correlation to the clinical response after identifying the most relevant immuno-monitoring techniques, demonstrating the immunological efficacy of DC immunotherapy in prostate cancer, which was performed after loading *ex vivo* DCs with proteic antigen; (iii) a clinical trial was carried out to evaluate the cell drug on patients with progressing prostate cancer. The patient's blood monocytes were transformed into effector monocyte-derived DCs, which fight the disease. The therapeutic cell drug comprised DCs loaded with cancer-specific antigens, activating the patient's immune system after re-injection.

EXPECTED AND OBTAINED RESULTS

Results showed an immune response following vaccination, plus signs of clinical responses in some of the patients. One patient showed complete regression of metastases four months after last vaccination, and another one showed stabilisation of the disease. The project team compared several technologies for obtaining DCs and chose to develop the most appropriate. Initial clinical results were confirmed via a randomised clinical study conducted in malignant melanoma stage 4 patients, immunised with DCs pulsed *ex vivo* with three melanoma cell lines lysates. Of the 49 patients, 14 initiated T cell immune response against the antigens presented and 10 patients had the disease stabilised; most of these immune responses and stabilisations were in the group of patients having received 6 vaccinations. Studies are continuing in colorectal and prostate cancer.

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LCVAC

NEW VACCINATION THERAPIES FOR LUNG CANCER

Acronym:	LCVAC
Project number:	COOP-CT-2004-512855
EC contribution:	€ 1 231 269
Duration:	24 months
Type:	Co-operative Research Projects
Starting date:	October 2004
Project website:	www.lcvac.org/

BACKGROUND

Lung cancer is the leading cause of cancer related mortality worldwide. In contrast to many other types of cancer, no significant improvements in treatment modalities of lung cancer have been achieved in the last decade. The major obstacles to its successful treatment include late diagnosis, heterogeneity of the tumors, highly metastatic behaviour, resistance to chemotherapy, and the failure to surgically remove all cancer cells.

A vaccine is essentially a form of purified antigen or mixture of antigens, together with immune-stimulating agents (adjuvants), administered to induce an effective immune response. Unfortunately, effective antigens specific to lung cancer cells are currently unknown. Also, lung cancers can be very heterogeneous and contain variations in lung cancer cell types increasing the difficulty of developing effective vaccines. The challenge is to find specific antigens,vaccine formulations and vaccination approaches in order to stimulate an effective immune response against the different lung cancer types.

AIMS

LCVAC's aims were:

- to identify and characterise novel lung cancer specific antigens using proteome analysis;
- to develop an effective and safe vaccination protocol for antigens and tumor cells;
- to characterise and generate human lung cancer cell lines to be used for an allogeneic cellular cancer vaccine.

EXPECTED AND OBTAINED RESULTS

Within the LCVAC consortium an important progress was made regarding the discovery and validation of new lung cancer specific antigens. Using differential expression studies and proteome analysis, the NCAM-MUM splice variant was shown to be a SCLC specific antigen and expression of the cytokeratin (CK) panel CK6/CK16 was found to be specific for the squamous cell carcinoma subtype of NSCLC. Both NCAM MUM and CK6/CK16 are promising markers to be used for lung cancer diagnosis and therapeutics. For NCAM MUM recombinant protein production procedures as well as QA/QC technologies evaluating the immunogenic potential have been developed within the scope of this project. NCAM MUM was shown to be immunogenic, inducing a clear cellular and humoral immune response in Balb/c mice immunized with the recombinant protein. Vaccination approaches were optimized and the infiltration of cells at the inocculum site was described in detail. Based on the cellular infiltration at the site of injection, alum absorbed multiple cytokine adjuvant was shown to be the best practice for recombinant protein immunisations. DNA immunization alone was shown to induce only a limited antibody response and no cellular immune response, whereas boosting with NCAM MUM recombinant protein induced a significant humoral and a MUM specific cellular immune response. The major results of this project are summarized in 3 scientific publications that are currently prepared for submission in peer-reviewed journals. Regarding the IPR, two patents are filed. We conclude that despite the fact that we have not been able to generate lung cancer cell lines for the development of an allogenic cellular lung cancer vaccine, we made important progress in the discovery and validation of new lung cancer specific antigens that are very promising for lung cancer diagnosis and treatment.

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VITAL

DEVELOPMENT OF OPTIMISED RECOMBINANT IDIOTYPIC VACCINES FOR SUBSET-SPECIFIC IMMUNOTHERAPY OF B CELL LYMPHOMAS

Acronym:	VITAL
Project number:	LSHC-CT-2006-037874
EC contribution:	€ 2 050 000
Duration:	36 months
Type:	STREP
Starting date:	1 January 2007
Project website:	www.cro.sanita.fvg.it/progetti/vital/index.htm

BACKGROUND

While therapeutic vaccines targeting B cell non-Hodgkin lymphoma (NHL) idiotype (Id) are proving their strength against these malignancies, their extensive use is impeded by the fact that they are patient-specific. This results in their complex and pricey individualised production. This project is using the molecular features of Id proteins of distinct B cell lymphomas/leukaemias to develop pre-made, recombinant Id proteins to vaccinate subgroups of lympho-proliferative disorders expressing molecularly correlated idiotypes.

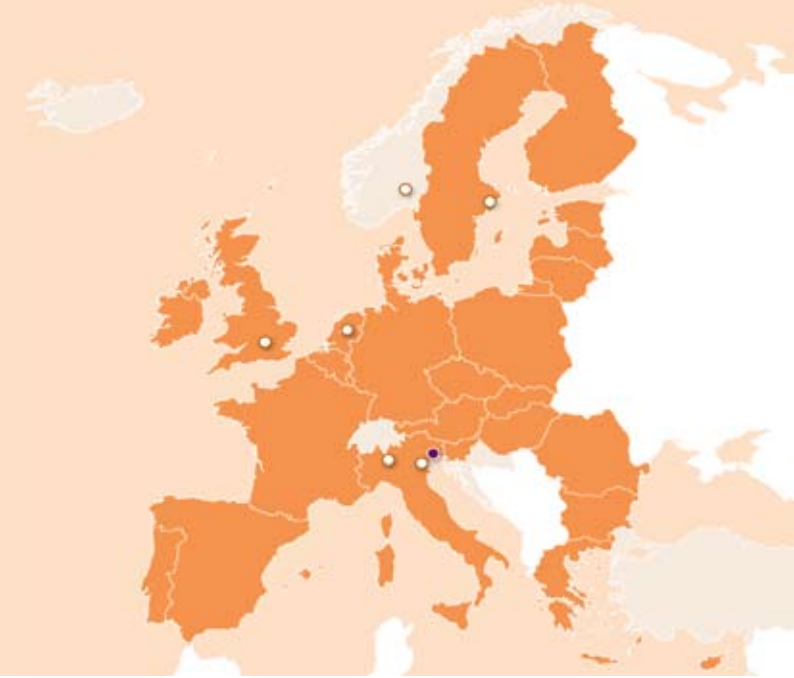
AIMS

A database is being built of Id sequences expressed by various B-NHL so as to identify subgroups of tumours expressing molecularly correlated Id proteins. VITAL will also do the following:

- characterise the selected Id proteins for their immunogenicity and for the ability to induce cross-reactive immune responses against related Id proteins;
- identify B and T cell epitopes;
- develop dedicated assays for immunomonitoring;
- produce optimised versions of selected Id vaccines (by using new strategies and validated in animal models);
- assess and validate new adjuvants and delivery systems for improved Id vaccine formulations and administration;
- generate and filter, based on GMP standards, the most promising Id proteins, which will then be included in new vaccine formulations for 'cross-reactive' immunotherapy trials;
- perform preclinical characterisation of the immunogenicity of selected natural Id proteins that can induce immune responses against lymphoma cells expressing molecularly correlated Id proteins.

EXPECTED AND OBTAINED RESULTS

It is expected that novel diagnostic and therapeutic tools will become available on both the European and international markets.



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MIMOVAX

ALZHEIMER´S DISEASE-TREATMENT TARGETING TRUNCATED ASS40/42 BY ACTIVE IMMUNISATION

Acronym:	MimoVax
Project number:	LSHB-CT-2006-037702
EC contribution:	€ 2.4 M
Duration:	36 months
Type:	STREP
Starting date:	1 October 2006
Project website:	www.mimovax.eu

BACKGROUND

There are 12 million cases of Alzheimer's disease worldwide and 3.5 million people in Europe are afflicted with it. It is believed that these figures will double in the next 20 years as the European population ages. Alzheimer's mostly affects people over 65 years of age and it is the most common form of dementia. There is currently no cure for the progressive neuro degeneration it causes. More research is urgently needed into its cause both for social and economic reasons. This project is focusing on the use of immune reactions to fight Alzheimer's, which is caused by deposits of amyloid-beta (Aβ) peptides which form into clumps (known as plaques). They develop when parts of a human protein detach from the cell membrane of nerve cells and stick together. The project is focusing on developing a vaccine that breaks down these cell clumps.

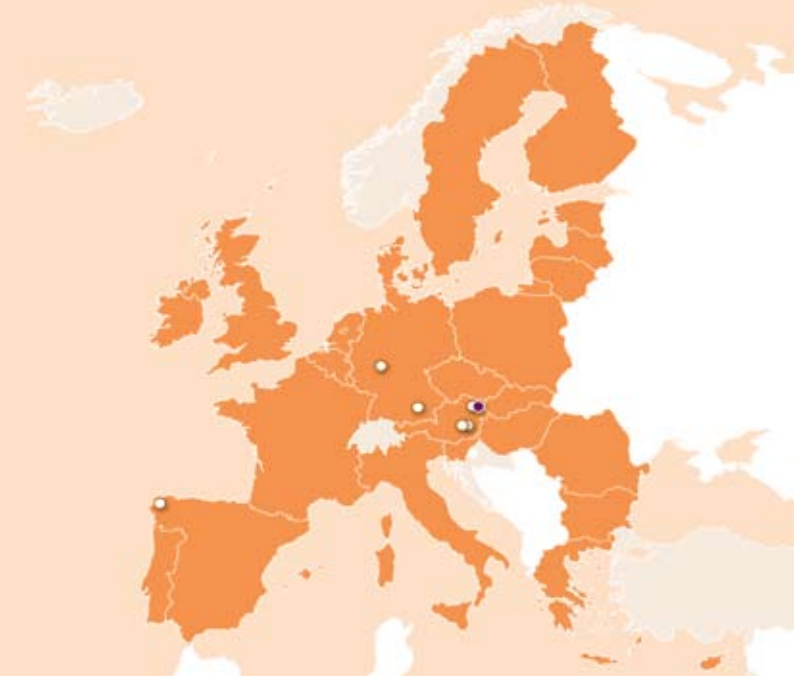
AIMS

The aim of MimoVax is to find a vaccine that will cure Alzheimer's. To do this the following objectives will be carried out:

- novel monoclonal antibodies directed against neo-epitopes on N-terminally truncated derivatives of Aβ will be generated and their specificities will be evaluated;
- mimotope peptides will be identified by screening peptide libraries followed by testing their suitability by assessing their *in vivo* immunogenicity in mice;
- mimotope-based vaccines will be formulated and evaluated for efficacy in animal models of Alzheimer's;
- *in vivo* imaging systems will be set up to analyse anti-Aβ antibody distribution and turnover in mice as well as effects of the novel Alzheimer's vaccine on plaque deposition in living transgenic animals;
- SOPs for manufacturing GMP material will be determined;
- vaccine conjugate formulation for subsequent analysis of toxicity and for the phase I clinical trial will be defined based on the experience from *in vivo* data obtained during the project;
- analysis of toxicity will be performed in mice according to standard toxicology protocols for vaccines to exclude detrimental side effects of the newly developed vaccines;
- a clinical phase I will be performed to analyse safety of the newly developed Alzheimer's vaccine in human patients.

EXPECTED AND OBTAINED RESULTS

The project expects to develop a safe Alzheimer's vaccine which can prevent or reverse neuro degeneration.



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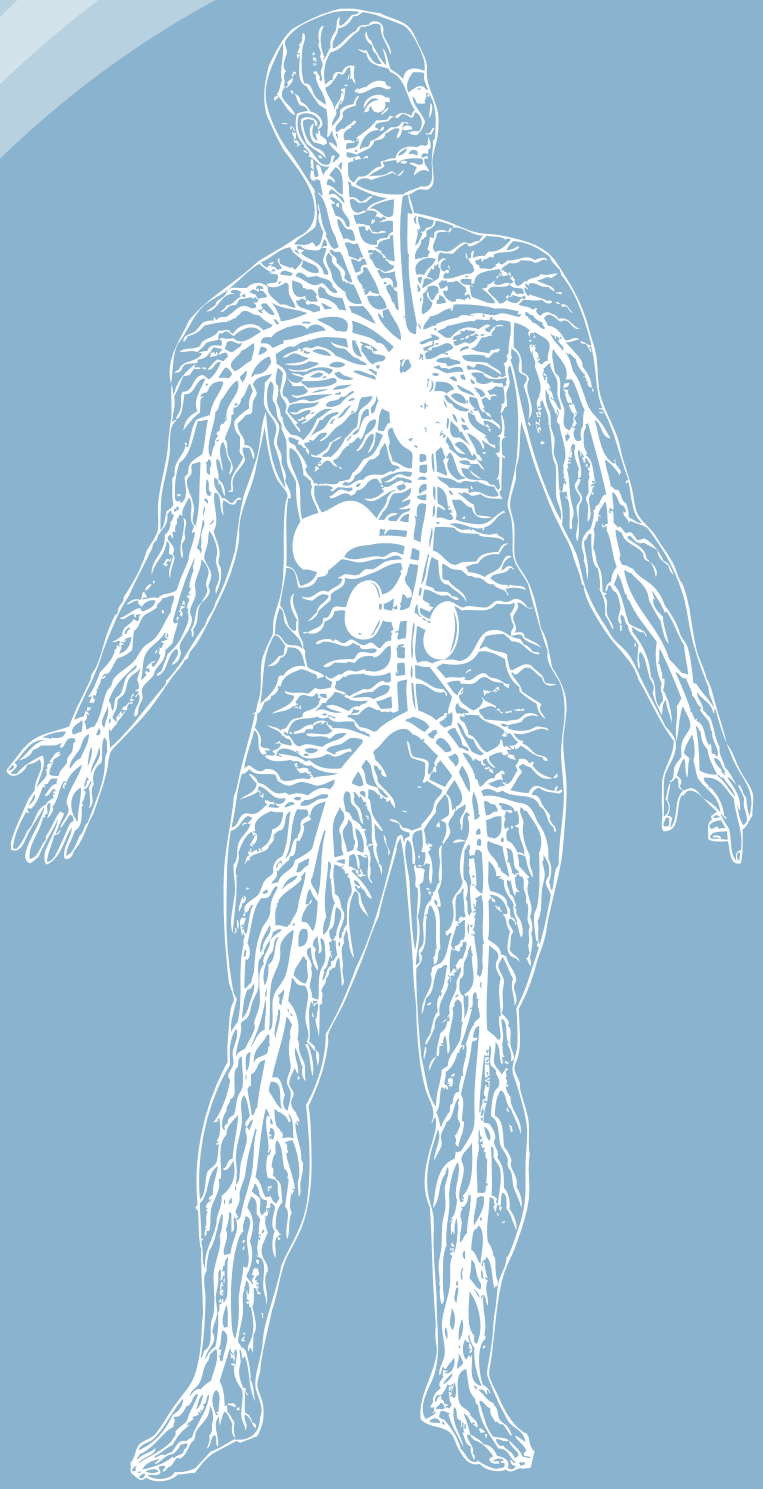
CLINICAL RESEARCH AND CAPACITY BUILDING



INTRODUCTION

CLINICAL RESEARCH AND CAPACITY BUILDING

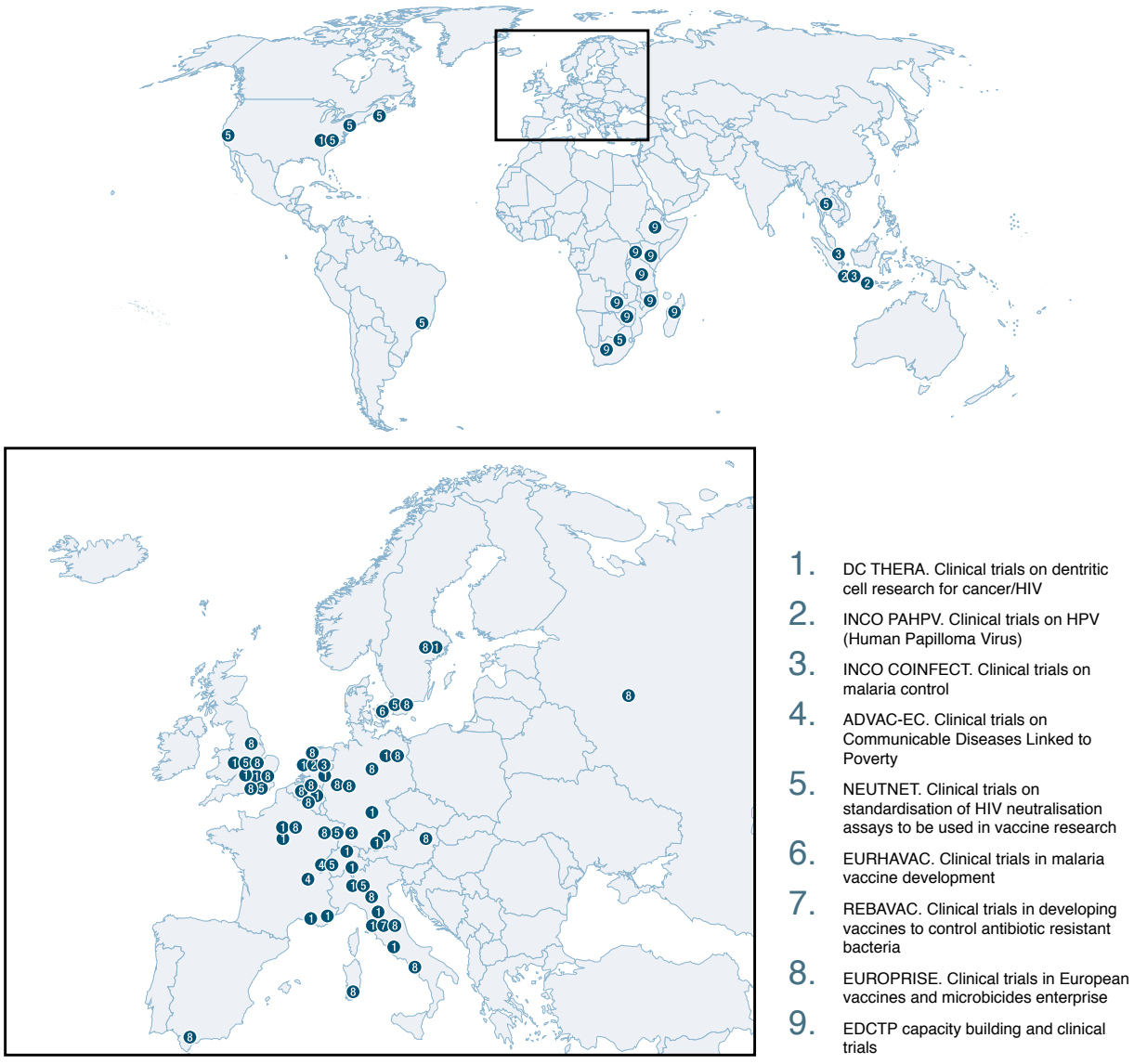
Many factors account for the revived global interest in vaccines including economic reasons and new scientific breakthroughs, but maybe the most important aspect is an increased realisation of public health potential. It makes sense to use vaccines to quell epidemics and pandemics, as mass vaccination is more tolerable and more cost-efficient than long-term care for patients with infectious diseases. Vaccination can thus contribute enormously to public health if implemented efficiently at the individual level. The actual implementation of new vaccines and improved use of existing vaccines is therefore a critical aspect to exploit vaccines maximally. This also includes training of researchers and health personnel in better understanding of vaccines and vaccinology.

The largest single initiative funded in health research in FP6 was the European and Developing Countries Clinical Trials Partnership (EDCTP). The EDCTP is dedicated to support capacity building and performance of phase II and III clinical trials in Africa for new treatments and vaccines against HIV/AIDS, malaria and tuberculosis. The EDCTP was established under article 169 of the European Treaty and upon a decision of the European Parliament and Council in June 2003. The EC has allocated EUR 200 million to the EDCTP, which was established in autumn 2003 as a separate legal entity in The Hague in the Netherlands. It aims is to integrate European scientists with sub-Saharan African countries in order to build clinical research capacity and to develop new treatments and vaccines against the three big infectious diseases. While the EDCTP will undertake a wide range of activities, a significant part will be directly linked to supporting clinical trials for new vaccine candidates or to building clinical capacity in Africa for future vaccine research.

The other major activity in clinical vaccine research is a better integration of clinical vaccine research in Europe in the HIV/AIDS field. The aim of the EUROPRISE network of excellence is to better synergise European research on new preventive technologies for HIV/AIDS, including both microbicides and vaccine research. The EUROPRISE network includes about 15 European research projects funded by both the European Commission and the Gates Foundation, representing more than 132 institutions from 22 countries.

Another NoE, DC-THERA, is focused on the clinical application of vaccines based on dendritic cells. This network will integrate the activities of 26 groups of scientists, clinicians and SMEs into an ambitious Joint Activity Programme to translate genomic, proteomic and bioinformatic information into useful endpoints for clinical trials of DC-based therapies for cancer and HIV.

Besides the above projects, this area also comprises a number of other activities which focus on networking of activities, harmonization of clinical activities or human capacity building through training of scientists. Although many of these activities have a relatively small budget, they have an important role in filling the gaps in many research activities or in building bridges in the scientific community.



1. DC THERA. Clinical trials on dentritic cell research for cancer/HIV
2. INCO PAHPV. Clinical trials on HPV (Human Papilloma Virus)
3. INCO COINFECT. Clinical trials on malaria control
4. ADVAC-EC. Clinical trials on Communicable Diseases Linked to Poverty
5. NEUTNET. Clinical trials on standardisation of HIV neutralisation assays to be used in vaccine research
6. EURHAVAC. Clinical trials in malaria vaccine development
7. REBAVAC. Clinical trials in developing vaccines to control antibiotic resistant bacteria
8. EUROPRISE. Clinical trials in European vaccines and microbicides enterprise
9. EDCTP capacity building and clinical trials

Fig. 4: Vaccines clinical trials information

EDCTP

EUROPEAN AND DEVELOPING COUNTRIES CLINICAL TRIALS PARTNERSHIP

Acronym:	EDCTP
Project number:	F169-CT-2003-980429
EC contribution:	€ 400 million
Duration:	84 months
Type:	Article 169
Starting date:	16 September 2003
Project website:	www.edctp.org

BACKGROUND

Disease prevention in Africa is a top priority, not only in order to help prevent millions of unnecessary deaths, but also to begin to free the continent from its perpetual disease-poverty-disease cycle, so it can begin to grow economically. The principal diseases devastating Africa are HIV/AIDS (human immunodeficiency virus/acquired immune deficiency syndrome), malaria and tuberculosis (TB), which are currently killing about 5 million people every year. About 2 million of these die from HIV/AIDS, for which there is as yet no cure. AIDS also forms a deadly partnership with TB, which is the leading cause of mortality in people who are HIV positive. Malaria kills about 1 million people in Africa every year and 500 million are infected annually.

These diseases put a huge economic burden on African families. People on very low wages incur huge debts and use up to a quarter of their annual income to pay for treatment for sick relations. If they are unable to save, they can never escape the poverty-disease trap. The high economic toll of the main diseases is also contributing to a decline in per capita income in many sub-Saharan African countries. When large numbers of the population are unable to continue working because of severe illness, harvests are not gathered, factories are less productive and children are put to work to replace sick adults, again perpetuating the poverty cycle.

Reducing the disease burden in Africa will take years of dedicated hard work and cooperation between European and African scientists and medical specialists. Proper organisation is also of key importance. Malaria and TB are both preventable and curable, but need long-term courses of treatment that must be followed strictly. However, this procedure is not always implemented and many patients do not complete their designated treatments. For there to be a serious reduction in curable diseases such as malaria and TB, health centres must be established with fully trained staff who keep registers of patients receiving treatment.

If the disease burden is to be lightened in Africa, long-term and coordinated programmes of action must be undertaken. To this effect, the EC Research Directorate General has set up a clinical trials programme funded under the Sixth Framework Programme, at EUR 400 million over 5 years. Experts from 14 EU countries plus Switzerland and Norway are working alongside African scientists and medical experts to launch the European and Developing Countries Clinical Trials Partnership (EDCTP), to help facilitate and develop clinical trials for new drugs and vaccines against HIV/AIDS, malaria and TB. The EC is taking an overarching role in the project, coordinating and bringing together expertise from all the participating countries.

AIMS

The Commission has funded research on HIV/AIDS, TB and malaria for many years. Over EUR 100 million was spent on research under the Fifth Framework Programme, for example, but now is the time for a more coordinated and integrated approach. Increasing the health of the populations of AIDS-stricken countries, thereby enabling them to break out of the poverty-disease cycle, and consequently creating more robust economic and social conditions are the overall aims of the project. These will be developed through networking and coordination of both European and African programmes and activities carried out in developing countries.

This is truly a joint programme, with European and African experts and institutes working together. African scientists and doctors are on the programme's steering committee and will take a vital part in the process, from the opening phases until the clinical trials stage. The drugs to be tested in the clinical trials will be selected taking into account the needs and the financial means of the recipients in terms of ease of use and affordability, and trials will be carried out in full accordance with ethical best practice.

Pharmaceutical companies provide over 60% of drugs used in developing countries, and many drug and vaccine candidates originate from private laboratories. However, a longstanding problem involving health programmes in developing countries is that it is not feasible for pharmaceutical companies to commit themselves fully to

developing drugs and vaccines for countries that may not be able to pay for them. The EC's intention is to solve this problem by using this programme to bridge the gap between the needs of developing countries and the pharmaceutical industry's need to make a profit.

EXPECTED AND OBTAINED RESULTS

The most important results of the programme will be the establishment of strong roots for future long-term cooperation between researchers and coordination of research projects and the development of exchange courses between European and African institutes and universities. The pooling of resources such as funding agencies, expertise and academic institutions will lead to alliances between European and African partners that will promote joint activities in training, research and capacity strengthening, leading to joint calls and policies.

It is hoped that the high visibility of the programme will help to secure support from scientific, clinical and political figures in African countries. This is vitally important in order to develop long-term local strategies to deal with disease and address the needs of both the people and the local healthcare systems. The programme will also help to establish a network of reference laboratories in Africa and to set up the training of health centre staff, who can carry out basic medical procedures. In terms of developing clinical trials, a long-term programme such as EDCTP will help to strengthen the regulatory environment for setting up clinical trials, improve the infrastructure for trial sites and strengthen human resources in trial sites and institutes.

Putting in place a solid information management structure will also be an important and long-term result of the programme. Resolving administrative issues, providing scientific support, facilitating external representation and communications, ensuring compliance with contractual obligations, supporting the setting up of clinical trials registries and developing tools for dissemination of knowledge are all vital components for building up a strong infrastructure for future projects.

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Capacity building and site development for the conduct of phase III trials of TB vaccines

Capacity building in preparation for the conduct of preventive HIV vaccine trials and phase III trials of TB vaccines

EUROPRISE

EUROPEAN VACCINES AND MICROBICIDES ENTERPRISE

Acronym:	EUROPRISE
Project number:	LSHP-CT-2006-037611
EC contribution:	€ 15 500 000
Duration:	60 months
Type:	NoE
Starting date:	1 January 2007
Project website:	www.altaweb.it/europrise/

BACKGROUND

The successful development of preventative strategies against HIV-1 infection (microbicides, vaccines or their combined effects) would provide a pivotal turning point in global efforts to combat the pandemic spread of AIDS, with an impact of incalculable value on societal problems associated with this disease. The principal aim of this project is to bring together EU scientists from the microbicide and vaccine fields to embrace a coordinated approach to HIV-1 infection prevention research.

Vaccines delivering non-replicating antigens mostly fail to induce sufficient mucosal responses and immunological memory to provide protection against high viral challenge. In contrast, while it may be technically easier to develop microbicides that prevent transmission when applied before intercourse, their duration of protection is likely to be short-lived and their efficacy will be critically dependent upon user compliance. To date, both fields have been slow to work together in the development of products that provide multiple levels of protection.

This network is focusing on the premise that microbicides and vaccines targeting multiple stages of mucosal transmission will have the best chance of success. Indeed, there are many reasons why the two fields should collaborate in developing effective strategies to prevent mucosal vaginal or rectal transmission, including the facts that approximately 80 % of new HIV infections are now heterosexual, and the main entry of infection is across the vaginal or rectal mucosa. Topically applied products are likely to have a high level of acceptance, and importantly, their use would be female-initiated. This is an important factor for women who have no means to protect themselves if their partners do not use condoms. Also, effective microbicides are likely to become available before effective vaccine candidates. Thus it is likely that in the near future all vaccine efficacy trials will be carried out in an environment where there is widespread use of vaginal microbicides. Consequently, it will be important to understand the interaction, and the potential interface of these different prevention technologies.

AIMS

The project has the following aims:

- standardisation and harmonisation of research tools;
- identification of new anti-HIV infection/AIDS vaccine and microbicide candidates and combinations to prevent HIV infection/AIDS;
- establishment of a clinical development pathway for vaccines and microbicides within a European framework;
- provision of scientific training in microbicide and vaccine development;
- facilitating access to information relevant to HIV-1 microbicides and vaccines;
- provision of a single focus for European HIV-1 microbicide and vaccine research.

EXPECTED AND OBTAINED RESULTS

The expected results are set out below:

- standardisation and harmonisation of research tools;
- the development of a portfolio of existing and new prevention candidates;
- facilitating basic HIV/AIDS research in into clinical trials;
- the increased integration of European research in the fields of HIV-1 vaccine and microbicide research;
- the development of an Internet resource.

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DC-THERA

DENDRITIC CELLS FOR NOVEL IMMUNOTHERAPIES

Acronym:	DC-THERA
Project number:	LSHB-CT-2004-512074
EC contribution:	€ 7 600 000
Duration:	60 months
Type:	NoE
Starting date:	1 January 2004
Project website:	www.dc-thera.org

BACKGROUND

Dendritic cells (DC) form part of the immune system and are found in most body tissues, particularly in the skin and lining of the gastro-intestinal tract. Their job is to process and ingest antigen material including foreign bacteria that invades the body. They control many types of immune response and consequently there is growing interest in using DC in HIV/AIDS and cancer research and many other diseases. Dendritic cell immunobiology has enormous potential for the development of new immunotherapies for cancer and infectious disease and this project focuses on these potentials.

AIMS

The project's aim is to facilitate the translation of genomic, proteomic and bioinformatic information with knowledge from molecular cell biology and pre-clinical models towards clinical trials of DC-based therapies for cancer and HIV. It will do this by an ambitious joint programme of activities, with the intention of restructuring the field of immunotherapy.

EXPECTED AND OBTAINED RESULTS

The network is translating genomic, proteomic and bioinformatic information, along with knowledge pertaining to molecular cell biology and preclinical models, into therapeutic endpoints, namely clinical trials of DC-based therapies for cancer and HIV.

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ENACT

EUROPEAN NETWORK FOR THE IDENTIFICATION AND VALIDATION OF ANTIGENS AND BIOMARKERS IN CANCER AND THEIR APPLICATION IN CLINICAL CANCER IMMUNOTHERAPY

Acronym:	ENACT
Project number:	LSHC-CT-2004-503306
EC contribution:	€ 4 166 513
Duration:	36 months
Type:	STREP
Starting date:	1 January 2005
Project website:	www.enactcancerresearch.org/

BACKGROUND

Cancer remains a major health problem with enormous economic, physical and emotional costs to citizens and the state. Latest statistics show that more than one in three people will develop some form of cancer in their lifetime. Along with cardiovascular disease it is the biggest source of health care costs and suffering in Europe.

Results from recent immunotherapy trials suggest that inducing tumour-specific T cell responses to tumour antigens, can cause the regression of tumours or the stabilisation of the disease in some patients. However, the mechanisms underlying the failure of immunotherapy to control and destroy residual cancer are not yet fully understood. Current knowledge of adoptive cancer immunity 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.

AIMS

This project aimed to identify markers of response and tumour antigens associated with ovarian, breast and prostate cancer, as well as melanoma progression and resistance to immunotherapy. A technological base was established for vaccine development (not necessarily restricted to cancer vaccines), and a better understanding of the basic biological mechanisms underlying antigen presentation and recognition of tumours by CD8+ and CD4+ T lymphocytes and NK cells emerged.

EXPECTED AND OBTAINED RESULTS

ENACT's results are set out below:

- identification of markers relating to the outcome of immunotherapy;
- clinical material and cancer cell lines for scientific investigation;
- cellular and humoral immune responses for patients undergoing immunotherapy;
- biomarkers using proteomics and computer-based algorithms;
- immunological, genetic and proteomic biomarkers as indicators of therapeutic response related to gender.

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ADVAC-EC

ADVANCED VACCINOLOGY TRAINING FOR SCIENTISTS FROM ACC AND DEVELOPING COUNTRIES: FROM GENOMICS TO VACCINATION STRATEGIES FOR COMMUNICABLE DISEASES LINKED TO POVERTY

Acronym:	ADVAC-EC
Project number:	LSSP-CT-2004-005106
EC contribution:	€ 390 000
Duration:	36 months
Type:	SSA
Starting date:	16 December 2004
Project website:	ADVAC.org

BACKGROUND

Spreading knowledge and practice of vaccinology in developing countries is a priority and with this aim the Mérieux Foundation and University of Geneva, partners of the ADVAC-EU project, organised an advanced vaccinology course for the duration of the project. The two-week course was held once a year and comprised top-level lectures followed by interactive discussions and specific practical exercises in small working groups. Focus was placed on vaccines against HIV, tuberculosis and malaria. The course promoted contacts and international networks development.

Funding from the EC ensured that scientists from developing countries, associated candidate countries, Russia, other newly independent states and the western Balkans benefited from fellowships for travel, housing and registration.

AIMS

The overall objective of the ADVAC-EU project was to create a critical mass of people, in Europe and in developing countries, with a sufficiently broad knowledge of vaccinology to be able to play a leading role in decision-making processes concerning the following:

- preclinical vaccine research (go/no-go);
- design and monitoring of clinical trials;
- vaccine safety issues;
- selection of new and appropriate vaccination strategies, including economic aspects and communication.

EXPECTED AND OBTAINED RESULTS

The expected result is the advancing of knowledge of vaccinology in Europe and in developing countries.

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NEUTNET

STANDARDISATION OF HIV NEUTRALISATION ASSAYS TO BE USED IN VACCINE RESEARCH AND CLINICAL TRIALS

Acronym:	NeutNet
Project number:	LSSP-CT-2004-012190
EC contribution:	€ 299 000
Duration:	27 months
Type:	SSA
Starting date:	1 January 2005
Project website:	www.sanraffaele.org

BACKGROUND

It is well established that antibodies play an important part in protection against viral diseases such as measles and influenza, but the role of neutralising antibodies in HIV-1 protection and pathogenesis remains to be further defined. Production of an antibody response with a broad neutralising activity against primary isolates of multiple HIV-1 subtypes continues to be a desired characteristic for candidate HIV vaccines. To support the evaluation of phase I, II and III human vaccine trials testing new HIV immunogens, it is important to standardise as far as possible and apply high-throughput specific and reproducible HIV neutralisation assays. Standardised HIV neutralisation assays make it possible to compare all vaccine efforts throughout the world.

AIMS

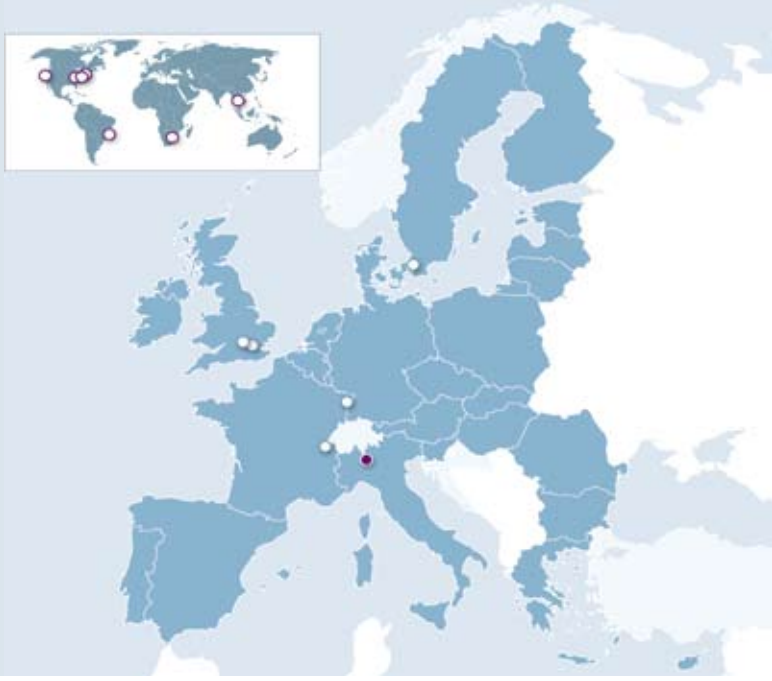
The project primarily aims to coordinate activities to standardise methods for the measurement of neutralising antibodies to HIV-1 to be used in vaccine research and clinical trials. Other aims are:

- developing and centralising the necessary reagents to undertake the study;
- preparing a draft protocol and guidelines for the study;
- organising an initial study to compare different neutralisation methods using a number of well-known monoclonal antibodies against a panel of well-characterised viruses;
- defining the methods for data analysis and statistical comparisons of assay results from the different participants;
- organising a subsequent study to compare polyclonal serologic reagents and defining the best conditions to determine neutralising activity;
- defining the needs of the scientific community involved in both preventive and candidate materials for evaluation;
- organising a workshop in collaboration with WHO/UNAIDS to discuss the results of the actions listed above and share the information with a larger body of researchers in this field.

EXPECTED AND OBTAINED RESULTS

The expected results of the project include:

- collection of reagents and materials for the study;
- development of a questionnaire for the collection of information about reagents and assays;
- definition of the statistical significance of the different methods;
- definition of the standards for neutralisation assay;
- international workshop on standards for neutralisation assays
- dissemination of SOPs and workshop proceedings.



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COINFECT

MALARIA AND COINFECTION: NEW INSIGHTS FOR MALARIA CONTROL

Acronym:	COINFECT
Project number:	INCO-CT-2006-031714
EC contribution:	€ 290 000
Duration:	24 months
Type:	SSA
Starting date:	1 October 2006
Project website:	www.coinfect.eu

BACKGROUND

Malaria and helminth infections often occur at the same time in tropical regions and their interaction can alter the course of the malaria infection and disease. Helminth infections alter the immune system affecting responses to third party antigens.The studies carried out so far seem to agree that helminth co-infections seem to either exacerbate or curtail the degree of malarial disease. New studies need to be carried out to gain in-depth knowledge of the interaction between these parasites in humans in the context of controlling malarial parasites and clinical disease.

AIMS

The overall aim of the project is to deliver the information and tools necessary for researchers in Asian countries to produce robust data on malaria and helminth coinfection and their immunological interaction. COINFECT will be used to transfer knowledge and technology between European, Malaysian and Indonesian experts in the area of malarial and helminth coinfection, in order to prepare a team with the ability to carry out high quality research in this important area. This will be achieved by:

- training in the setting up of specific epidemiological studies;
- developing questionnaires;
- training medical staff in clinical assessment;
- training in malarial diagnosis quality control;
- training in helminth diagnosis quality;
- standardised procedures for collection of blood by finger prick;
- demonstration of immunological methods that measure antibodies and cytokines;
- demonstration of molecular biological methods that measure gene expression by quantitative PCR and determine genetic polymorphisms.

Pilot study:
The trained personnel will carry out pilot studies to determine the prevalence of malarial and helminth coinfections and the immunological interaction between these two infections.

EXPECTED AND OBTAINED RESULTS

The results are expected to include:

- trained clinicians and nurses in Indonesia and Malaysia;
- trained researchers with expertise in high quality diagnosis of malaria and helminth infections using quantitative PCR;
- trained scientific staff to perform antibody measurements and interpret them;
- staff able to perform and interpret cellular and molecular immunological tests;
- scientists with up to date knowledge of genetic studies and methodologies;
- trained scientific staff able to analyse data;
- trained scientists who are able to collect accurate data on malaria and helminth coinfection; consent forms for study participants;
- questionnaires specific for estimating prevalence of severe malaria in communities;
- SOPs for all immunological tests;
- database templates for collection of (immuno) epidemiological data on coinfection;
- results of the pilot study.

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EURHAVAC

EUROPEAN NETWORK FOR HARMONISATION OF MALARIA VACCINE DEVELOPMENT

Acronym:	EURHAVAC
Project number:	LSHP-CT-2006-018860
EC contribution:	€ 260 000
Duration:	24 months
Type:	SSA
Starting date:	1 December 2006
Project website:	www.emvi.org/eurhavac

BACKGROUND

Malaria vaccines require a series of coordinated steps ranging from basic research and identification of lead vaccine candidates to evaluation for safety and immunogenicity in Europe before they can be clinically tested in Africa for safety, immunogenicity and efficacy. Before licensure, these vaccines will be tested in large multicentre trials on thousands of people, as required by national and EU regulatory authorities. There has been considerable investment at national and EU level in malaria basic research, but this has not been matched by investment in moving experimental vaccines through manufacturing and clinical testing. Common guidelines on harmonised preclinical and clinical evaluation and agreed decision-making criteria are needed to provide a more rational basis for the development of malaria vaccines.

This project is sharing information and identifying and prioritising the most critical scientific, technical and regulatory questions. It will be the basis for the implementation of common standards for assessing research results.

AIMS

The project's aims are as follows:

- the definition and implementation of decision-making processes for pharmaceutical development;
- the definition and implementation of a clinical development strategy;
- the harmonisation of the evaluation criteria for malaria vaccines;
- the dissemination of knowledge and information yielded by the three first action plans.

EXPECTED AND OBTAINED RESULTS

The project is helping to create an enabling environment capable of coordinating resources - available in the European Research Area - into a network proficient in managing the existing and desired knowledge. Such knowledge management will provide for the development of strategice approaches to malaria vaccine development and evidence-based benchmarking.

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PAHPV-1

HPV PILOT ACTION INDONESIA

Acronym: PAHPV-1
Project number: INCO-CT-2004-502455
EC contribution: € 129 000
Duration: 16 months
Type: SSA
Starting date: 16 April 2004

BACKGROUND

HPV (Human Papilloma Virus) is the most common sexually transmitted disease. Infection of the uterine cervix with oncogenic HPV types (e.g. HPV16, 18, 31, 33, and 45) occurs in 80% of sexually active women, mostly in developing countries, and large prospective studies show that acquisition of HPV from male partners is common. Progressive HPV-related diseases cause 233 000 deaths worldwide per year.

In this pilot action, Leiden University Medical Center and its counterparts in Indonesia (Jakarta and Bali) ran a clinical trial programme of 200 women to chart the percentage at risk for progressive HPV 16 as well as the immune response to this HPV type. For this purpose, the feasibility of a simple, low-cost DTH skin test to detect HPV-immune reactivity was examined. Once the DTH skin test proves useful for detecting protective immune responses against HPV16 it will become accessible to other developing countries and will be helpful in the selection of individuals in need of specific vaccination.

AIMS

The aims of the project were as follows:

- to collect epidemiological data on the incidence of HPV16 and the immune status against the virus in preparation for a future HPV vaccination programme;
- to include HPV education and screening in current STD campaigns in Jakarta and Bali and share the experiences with HPV researchers in other developing countries.

EXPECTED AND OBTAINED RESULTS

It is anticipated that the project will generate new information on the epidemiology of HPV types and infection rates. The results of the study will enhance the knowledge of HPV infections in Indonesia, in combination with the HPV-specific immunological status in healthy women and patients with cervical HPV-related disorders.

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REBAVAC

NOVEL OPPORTUNITIES TO DEVELOP VACCINES TO CONTROL ANTIBIOTIC RESISTANT BACTERIA: FROM THE TRIALS BACK TO THE LABORATORY

Acronym:	REBAVAC
Project number:	LSHM-CT-2006-037163
EC contribution:	€ 121 200
Duration:	12 months
Type:	SSA
Starting date:	1 September 2006
Project website:	www.altaweb.eu/rebavac

BACKGROUND

Antibiotic resistant bacteria are rapidly spreading worldwide, making it increasingly difficult to treat infections in large communities and, therefore, creating a major public health problem. Vaccination appears to be the best way to stop the spread and development of antimicrobial resistant micro-organisms. However, the analysis of the effects of using conjugated vaccines against *Spn, Haemophilus influenzae b (Hib)* and *Neisseria meningitidis (Men)* has shown a number of paradoxes and some interesting aspects that have led to a re-think about how immunity to polysaccharide is elicited following vaccination, and how memory is acquired. REBAVAC was a workshop which discussed the implication of the above-mentioned results and the results of ongoing research on the use and development of vaccines to fight antibiotic resistant bacteria.

A careful analysis of the results of past and current vaccination trials was necessary to design novel vaccines or vaccination strategies which can be developed as a main tool to fight antibiotic resistance.

AIMS

At the workshop the world's most important experts in vaccinology and immunology met healthcare providers, industry representatives and public health experts and discussed the key issues outlined above, including how to use and improve currently available conjugate polysaccharide vaccines to fight antibiotic resistant bacteria, and how better to understand the contribution of innate and adaptive components of the immune system in eliciting and boosting immune responses to conjugate vaccines.

EXPECTED AND OBTAINED RESULTS

The workshop will help European and international research and industry move towards more efficient/efficacious vaccines and vaccination strategies, and find novel immunisation methods for optimising the use and formulation of currently available vaccines that can fight antibiotic resistance.

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European Commission

Vaccines for Humans Research funded by the European Union

Luxembourg: Office for Official Publications of the European Communities

2008 — 176 pp. — 21.0 x 29.7 cm

ISBN 978-92-79-09455-2
DOI 10.2777/84341

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KI-81-08-337-EN-C

Europe has a long and successful tradition for vaccine research in both public and private institutions. Two-thirds of global vaccine R&D is being conducted by European organisations and almost 90% of all vaccine production takes place in Europe. Europe is therefore well positioned to take on new challenges in vaccine research, and exploit the immense opportunities that are opening up in this field of science. The European Commission's Sixth Framework Programme for Research (FP6) has been an important catalyst in this direction and has provided substantial momentum to further advance the European activities in vaccine research.

This publication compiles the projects on human vaccine research that were initiated during FP6 (2002-2006). Most of the projects have been funded through the Health theme of FP6, although important contributions came from the Food theme, the Information Society theme (IST) and from cross-cutting activities on international cooperation (INCO), and the support activities to small and medium-sized enterprises (COOP). Many of the projects will not conclude before 2009 or later, but they are already beginning to deliver important results. Taken together they provide evidence of a vibrant, visionary and ambitious research community, where hundreds of scientists are working together to discover and develop new vaccines for the world.

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ISBN 978-92-79-09455-2
9 789279 094552