

SMEs go LifeSciences – Projects under preparation

2. COMBATING MAJOR DISEASES

a) Applications-orientated genomic approaches to medical knowledge and technologies

Studying human development and the ageing process

- LSH-2005-2.1.4-1: Integration of research in development and ageing - NETWORK OF EXCELLENCE
- LSH-2005-2.1.4-3: Understanding the responsiveness of elderly people towards vaccination and infectious diseases - STREPs dedicated to SMEs

Projects # 72, 103, 104.

Project #72

Project #72 - Newbiotechnic S.A. - Spain

Date: 2005/04/05	Deadline: 2006/11/09
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Familiar with the European Framework Programme? **YES**

PROJECT

Title: Production of bioactive peptides for health using microorganism fermentation of agrifood byproducts	Acronym: AGRHEALTH
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Project type	STREP
Status	Planned for submission
Call references	Call 4th

Priorities' Main Research Areas	<ul style="list-style-type: none"> - Application of knowledge and technologies in the field of genomics and biotechnology for health - Combating major diseases
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Workprogramme Topic (according to each priority workprogramme)	<ul style="list-style-type: none"> - Rational and accelerated development of new, safer, more effective drugs including pharmacogenomics approaches - Understanding the responsiveness of elderly people towards vaccination and infectious diseases
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Project description

The project will focus on the valorisation of Agriculture and Agrifood Industry by products applying fermentation processes where enzymes (proteases) will produce peptides with bioactive properties for human health.

The proteases to be used in the project have been identified in the functional genomic project TRICHOEST (EU FPV). The project will also focus on the screening of other microbial biodiversity collections to identify new proteases able to produce new bioactive peptides for human health. Clinical trials will be performed to test antioxidant properties, antiaging, anticholesterol, anti-inflammatory and anticarcinogenic effects and cardiovascular protection.

Keywords	Human Health, Biomaterial, Bioeconomy, Genomics, Valorisation of byproducts, Cardiovascular diseases, Cancer, Aging, Immunomodulation		
Partners already involved	Sevilla University (Sevilla, SPAIN) Spanish Research Council (CSIC)-Fat Institute, Sevilla, SPAIN Newbiotechnic S.A. (NBT)		
Project budget (for the running projects)	nc	Budget reserved for SMEs	nc

Research topics

- LSH-2005-1.2.1-3: Rational and accelerated development of new, safer, more effective drugs including pharmacogenomics approaches - STREPs dedicated to SMEs

- LSH-2005-2.1.4-3: Understanding the responsiveness of elderly people towards vaccination and infectious diseases - STREPs dedicated to SMEs

Profile of SME sought

Role	technology development, demonstration, other
Country /region	Any country/region
Start of partnership	mid-term
Expertise required	Clinical trials in areas of aging, cancer, immunogenicity, cardiovascular diseases, biomedical products commercialisation

Project #103

Project #103 - Universidad Pablo de Olavide - Spain

Date: 2005/06/23	Deadline: 2005/11/09
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Contact

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Familiar with the European Framework Programme? **YES**

PROJECT

Title: Research in development and ageing	Acronym:
Project type	Network of Excellence
Status	Planned for submission
Call references	Call 4th

Priorities' Main Research Areas	<p>Cell cycle control Role of Hsp90 in cell cycle control and ageing</p> <p>Regulation of Coenzyme Q biosynthesis in eukaryotic organisms Genetics of coenzyme Q deficiency in humans</p> <p>Coenzyme Q synthesis in <i>Saccharomyces cerevisiae</i> and its implications in lifespan and ageing</p>
Workprogramme Topic (according to each priority workprogramme)	LSH-2005-2.1.4-1

Project description

Different approaches:

1) Understanding the mechanisms controlling the cell division cycle is an important landmark in modern biology. In higher eukaryotic organisms, cell cycle regulation is a basic event in development where multicellular organisms are generated by controlled cell division and differentiation, and in understanding oncogenesis (abnormal cell divisions). Within this topic, our end focus on the characterization of new cell cycle control genes identified by our group using yeast as a model organism. In particular, we study new mechanisms coordinating entry into mitosis and other cellular events such as cell growth and cytokinesis. In addition, we also use the nematode *C. elegans* to assay the role of the identified genes in processes such as development and aging.

2) Using the fission yeast *Schizosaccharomyces pombe* as our model organism our group (started very recently) tries to reveal the role that Hsp90 plays in cell cycle regulation and ageing. Using Genetics, Biochemistry and Cellular Biology techniques we analyze the effect of mutations in Hsp90 in the commitment to mitosis and cytokinesis, alone or in combination with other cell cycle mutations. We have identified physical interactions between Hsp90 and cell cycle proteins, probably reflecting the existence of Hsp90 complexes and we are now trying to purify such complexes. Finally, we are checking whether the ageing retardation effect described in *C.elegans* for Hsp90 mutants is a universal phenomenon also present in *S.pombe*.

3) The object of our work is to determine the mechanisms that regulate CoQ biosynthesis and the possible modifications in human fibroblasts isolated from ataxic patients showing a primary deficiency of CoQ. We use *C. elegans* and cultured human cells as research models. We have demonstrated by RNAi the participation of eight genes (coq1 to coq8) in CoQ biosynthesis in *C. elegans*. We have cloned these genes and have generated nematode stable strains harboring a construction that includes the sequence of one coq gene, the sequence of the endogenous promoter, and the sequence of GFP. We will use these strains to study the expression pattern of these genes throughout nematode life, especially in aging and early development. We have detected a primary deficiency of CoQ in fibroblasts isolated from ataxic patients and we are studying the functional complementation of cloned from these cells to determine the cause of deficiency. Further, we are working in the hypothesis that the nuclear activation of caspase3 can induce an increase of mitochondrial CoQ biosynthesis as a mechanism of cellular survival.

4) The aim of our research is double. We are analyzing expression of genes involved in the coenzyme Q biosynthesis pathway. At a transcriptional level we are monitoring its expression by competitive RT-PCR in different growth and oxidative stress conditions. We plan cloning and analyzing the promoter region to search for consensus sequences related to stress response. At a translational level, the expression of COQ genes during growth and in response to oxidative stress conditions will be performed with antibodies that we are developing. That study, immunoprecipitation analysis and FRET will be performed to study the interaction between the products of COQ genes required for the assembly of the coenzyme Q biosynthetic complex.

A second aspect of our research is focused in the study and characterization of an orphan gene of *Saccharomyces cerevisiae* encoding for a cytochrome b5 reductase located at the plasma membrane. This enzyme catalyzes coenzyme Q reduction using electrons from NADH. This enzyme modifies substantially the ratio NAD⁺/NADH producing a significant increase of the lifespan in these yeasts. Recent studies have shown that the action of this protein increasing lifespan requires the presence of the protein Sir2p, a histone deacetylase NAD⁺-dependent that blocks ageing produced by the ERCs accumulation (extrachromosome DNAr circles). Our aim is to perform a biochemical characterization of this protein, demonstrate its involvement in the life-span extension during caloric restriction processes and oxidative stress conditions.

Keywords	Ageing, Developmental biology		
Partners already involved			
Project budget (for the running projects)	nc	Budget reserved for SMEs	nc

Research topics

- LSH-2005-2.1.4-1: Integration of research in development and ageing - NETWORK OF EXCELLENCE

Profile of SME sought

Role	technology development, research, dissemination, demonstration
Country /region	Any
Start of partnership	start-up phase
Expertise required	The aim of the project is to determine the influence of genetic, environmental, and stochastic effects during development on the ageing process. The project should integrate the corresponding research in invertebrate and vertebrate model systems and their application in humans.

Project #104

Project #104 - Institute for Biomedical Aging Research of the Austrian Academy of Sciences - Austria

Date: 2005/06/23	Deadline: 2005/11/09
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Contact

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Familiar with the European Framework Programme? **YES**

PROJECT

Title: Understanding Immunosenescence for More Effective Vaccination in the Elderly	Acronym:
Project type	STREP
Status	Planned for submission
Call references	Call 4th
Priorities' Main Research Areas	LSH-2005-2.1.4-3
Workprogramme Topic (according to each priority workprogramme)	Understanding Immunosenescence for More Effective Vaccination in the Elderly

Project description

In 2002, we submitted the following Letter of Interest to the EU commission when asked for project ideas for the 6th framework. Now the text has been published as SME-STREP in the 4th call (see above). The project is still of great relevance, but, as we originally did not plan SMEs to participate, we are now urgently looking for partners.

The text of the Letter of Interest was as follows:

Understanding Immunosenescence for More Effective Vaccination in the Elderly

Introduction

Increased occurrence of infectious diseases in the elderly

It is widely known that the elderly population is more susceptible to several infectious diseases.

Clinicians have reported increased occurrence of bacterial infections (including pneumonia, urinary tract, skin and soft-tissue) as well as viral infections (including reactivation of herpes zoster and increased morbidity and mortality due to influenza and/or respiratory syncytial viruses) in the elderly. The socioeconomic burden of both influenza and pneumococcal infection in the elderly have been well studied and together they represent the sixth leading cause of death in the US.

An estimated 9-10% of the world's population may develop symptomatic influenza infection each year and the incidence is even higher in the elderly population where infection rates may reach as high as 43-60% in nursing homes. The cost estimates associated with these rates of infection are of course significant. In the USA influenza is believed to result in \$1-3 billion in direct costs as well as up to \$10-15 billion in indirect costs each year. Similar estimates have been made for the costs in Germany during an epidemic where losses to society were estimated at approximately DM 25.8 million in direct costs and DM 120 million in indirect costs and in France where direct costs were estimated at FF1.9 billion and indirect costs at FF14.3 billion per year.

Pneumococcal infection remains as the leading cause of community acquired pneumonia among adults (resulting in 30-50% of cases requiring hospitalization) and is particularly threatening for the elderly who are at higher risk of developing invasive disease where mortality rates can reach 20-40%. Infection rates with pneumococcus are estimated at 0.7-18 per 1000 population and the incidence of invasive pneumococcal disease is estimated at 50-60 cases per 100,000 elderly persons in developed countries. The cost associated with this infection rate is estimated at \$18 billion per year in the US.

Vaccination as a strategy to prevent morbidity/mortality in the elderly

Influenza- and streptococcus pneumonia-associated morbidity and mortality can be reduced in the elderly population by the use of appropriate vaccines. In this regard, the greatest single factor which can reduce the cost of influenza to individuals and society is prevention based on effective vaccination. Studies of cost effectiveness have shown that influenza vaccination is cost effective in all age groups but particularly among the elderly population where a direct savings of approximately \$117 per person per year was demonstrated. This is despite the fact that the influenza vaccine has lower efficacy among the elderly (approximately 56% effective for prevention of influenza-related respiratory illness, 50% effective for prevention of hospitalization, 68% effective for prevention of death) compared to young adult populations where protective efficacy numbers range from 70-90%. Similarly, the pneumococcal vaccine has been shown to be cost-effective and cost saving for people 65 years or older (\$121 savings) despite the fact that the efficacy (versus prevention of invasive disease) remains at 50-70% for the immunocompetent elderly. Estimates of the cost-effectiveness of the pneumococcal vaccine in the elderly suggest a cost per life-year gained of \$1800. Thus, if vaccine efficacy in the elderly could be further improved, the economic savings associated with vaccination against influenza, pneumococcus, and other infectious diseases could be even more important.

Poor vaccine response in the elderly and aging of the immune system

Despite limited success with specific vaccines devised for the elderly (e.g. influenza and streptococcus pneumonia vaccines), significant efficacy issues remain in this population which almost certainly result, at least in part, from the aging of the immune system. The aging of the immune system, referred to as immunosenescence, is associated with a dramatic reduction in responsiveness as well as functional dysregulation of the immune system. This deterioration of immune function with advancing age contributes to the increased incidence of morbidity and mortality from infectious diseases among the elderly, and possibly autoimmunity and cancer. Though marginal alterations in B-lymphocytes are apparent, the dramatic decline in humoral and cell-mediated responses is predominately the

consequence of senescent T cells. Two hypotheses have been advanced to explain the decrease of T cell response observed in the elderly. The first of these proposes that aged-associated changes in T-cell activity are due to the accumulation of replicative-senescent lymphocytes within the T-cell pool of elderly individuals. The second hypothesis speculates that gradual change in T cell biochemistry leads to an altered signal transduction pathway in the individual aged T cell. Most likely, the most accurate description of the aging effect on T lymphocyte activity combines elements of both hypotheses. A better understanding of the immunosenescence process and the characterization of its impact on the immunological response to specific vaccines would help to devise new strategy for more efficacious vaccination in the elderly. Clearly, the public health and socioeconomic impacts of such improvements would result in a healthier elderly population.

Project objectives

1. Vaccination of a large cohort of elderly individuals with influenza (split vaccine) and streptococcus pneumonia (plain PS vaccine).
2. Identification of elderly individuals exhibiting clinical susceptibility to influenza and/or streptococcus pneumonia infections. This selection will be done on the basis of an epidemiological follow-up investigating the occurrence of both infections. The occurrence of respiratory syncytial virus infections would also be included.
3. Identification of elderly individuals exhibiting immunological non-responsiveness on the basis of serological screening for influenza and/or streptococcus pneumonia antigens. A comparison between immunological non-responders and clinically susceptible individuals will be performed in order to determine whether an overlap exists between the two groups.
4. Characterization of pre- and post-vaccination cellular and humoral immune responses specific for influenza or streptococcus antigens in a sub-cohort of clinically susceptible or/and immunologically non-responder elderly individuals. This approach ultimately aims to determine which aspect(s) of the immunosenescence process is responsible for the poor efficiency of vaccination in the elderly.
5. Devise novel assays (based on proteomics/genomics technology) defining non-responsiveness/susceptible phenotype to influenza, streptococcus pneumonia, or respiratory syncytial virus.
6. Identify new strategies on the basis of the knowledge gained from the present study to compensate identified immuno-dysfunction(s) and therefore improve vaccine efficiency in the elderly

Project feasibility

The present project would start by the vaccination of a large cohort of elderly individuals with influenza (split vaccine) and streptococcus pneumonia (plain PS vaccine). An epidemiological follow-up investigating the occurrence of both infections as well as respiratory syncytial virus infection would then be used as a tool to select clinically non-protected elderly individuals against influenza and/or streptococcus pneumonia infections. Moreover, elderly individuals exhibiting immunological non-responsiveness will be identified on the basis of serological screening for influenza and/or streptococcus pneumonia antigens. A comparison between immunological non-responders and clinically susceptible individuals will be performed in order to determine whether an overlap exists between the two groups. This initial step would be performed at clinical centers in 8 to 10 European countries. A sub-cohort of clinical non-protected or/and immunological non-responder elderly individuals would then be the focus of a collaborative investigation into the immune mechanisms responsible for their lack of protection to influenza, respiratory syncytial virus or streptococcus pneumonia infections. These studies would mainly consist of cellular and humoral immunological studies to be performed on pre- and post-vaccination blood samples by five to six basic research institutions in different European countries that have well established expertise in these areas. Susceptible individuals would be further screened for a possible non-protection against other relevant infectious diseases in the elderly such as tetanus and diphtheria. Vaccine manufacturers should participate to provide vaccines (and adjuvants, see below) and material for basic research studies. Altogether, clinical protection as well as cellular and humoral immunity data will be used for the development of novel assays (including proteomics/genomics technology approach) that would better define non-responsiveness/susceptible phenotype to relevant infectious diseases in the elderly. Genomics and proteomics methodologies would be performed by one or maximally two central facilities. New strategies to compensate immunosenescence will be then considered. Several adjuvants with different impacts on the humoral and/or cellular immune compartments have been identified.

Furthermore, the efficiency of these new adjuvants has been demonstrated in human clinical trials. Therefore, on the basis of the knowledge gained from the present study, specific adjuvants will be selected and used to improve protection following influenza and streptococcus pneumonia vaccinations. These proposed formulations would be tested in preclinical models to assess their immunogenic potential and to validate when possible the formulation selection. The impact on various immune functions would be assessed in the preclinical models to confirm the predictions prior to clinical testing. Selected new formulations would be tested clinically in adult and elderly populations with a specific focus on augmenting protective response in the elderly population. Based upon the demonstration of clinical feasibility with the influenza and streptococcus pneumonia vaccines, new recommendations for vaccination strategies for the elderly will be defined for application to other vaccines specifically targeting this population (e.g. respiratory syncytial virus, tetanus and diphtheria toxoid).

Multidisciplinary and integration

A multidisciplinary scientific network is a prerequisite to take this crucial area of work forward. The authors of this project have already identified individuals with specific competencies including clinician/investigators, vaccines and adjuvants providers, both cellular and humoral immunologists with expertise in immunosenescence, and finally entities specialized in genomics/proteomics with expertise in immunology. This is the first time that a EU proposal aims to integrate these competencies into a large EU collaborative structure, which is a **necessary step to tackle the impact of immunosenescence on vaccination in the elderly.**

Keywords	vaccination, elderly, immunology, epidemiology, influenza, pneumonia, public health, diagnostics in immunology, antibodies, T cells, adjuvants		
Partners already involved	Andreas Thiel (German Rheumatism Research Centre, Berlin), David Goldblatt (University College London), Sergio Romagnani (University of Florence), if possible Tissuegnostics (Vienna)		
Project budget (for the running projects)	nc	Budget reserved for SMEs	nc

Research topics

- LSH-2005-2.1.4-3: Understanding the responsiveness of elderly people towards vaccination and infectious diseases - STREPs dedicated to SMEs

Profile of SME sought

Role	technology development, research, dissemination, demonstration
Country /region	Europe
Start of partnership	start-up phase
Expertise required	interest in vaccination and/or the immune system in the elderly