

Health and Biotechnology (BIOSAN)

including the extension “Medical aspects of Ageing (PROVIE)” (see priority D)

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1) Introduction

The Health and Biotechnology (BIOSAN) Programme of Research comprises two phases:

In a first call for project proposals launched in 2001 the three main priority areas of research were cancer, cardiovascular disease and immune intervention (see focal areas A-C of this programme).

A second call, to be launched in 2003, will concentrate on research into the medical aspects of ageing (research area D of this programme).

The research areas E-G on expression libraries, epidemiology and intelligent IT environments in the field of health will qualify for both calls for projects, but must relate to the specific subject areas of the call in question.

The BIOSAN Programme sets out to achieve qualitative improvements in the prevention, detection and treatment of cancer, cardiovascular disease and the diseases of old age, and to help develop new strategies for specific modulation of the immune system. The programme should boost the volume of biomedical research done in Luxembourg and make it more competitive, in terms both of basic and applied research and of the new biotechnologies deployed in health care.

Objectives

The commonest causes of death in the developed world are cerebrovascular accident (stroke), cardiovascular disease and cancer. Statistical studies conducted by the Health Ministry on the leading causes of death in Luxembourg confirm these international findings.

Thus a very sizeable proportion of the most active population is affected by these pathologies, and morbidity, or premature mortality have major repercussions for society and the economy.

Consequently biomedical research aimed at improving the prevention, diagnosis and treatment of these conditions remains an important priority for the nation's health.

To begin with, the BIOSAN Programme will thus seek to develop new scientific expertise, to achieve qualitative improvements in the prevention, detection and treatment of cancer and cardiovascular disease and to improve the potential benefits provided by immunotherapy.

During a second phase the BIOSAN Programme will seek to consolidate, network and promote research into the diseases of old age, and more specifically their epidemiological, psychosocial and biological aspects.

2) Programme priorities

A. Cancer

The WHO's Programme on Cancer Control tells us that from 2020 there will be 20 million new cases of cancer a year. In Luxembourg, the *Registre Morphologique des Tumeurs* (cancer register) records some 2000 new cases a year, the highest incidences being of prostate and breast cancer. Despite sophisticated new techniques in surgery, radiotherapy, chemotherapy and more recently immunotherapy, a considerable amount of basic research work will have to be done if we are to make progress in preventing, diagnosing and treating cancer.

Prostate cancer is the commonest male cancer in Luxembourg (Lamy et al, 1998), as it is in most countries of Europe. Its incidence in Luxembourg in 1995 was 110 cases per 100 000 men, compared with 70 for colorectal cancer and 50.8 for tracheobronchial cancer (*Registre Morphologique des Tumeurs*, Luxembourg, 1995). Breast cancer is the commonest female cancer in Luxembourg. One woman in ten will develop breast cancer during her lifetime.

Cancer is thus an area of concern to the national health authorities.

The BIOSAN Programme selectively targets cancer, one of the commonest pathologies seen in Luxembourg.

Key actions:

A.1 Cellular and molecular mechanisms of tumorigenesis and metastasis

- *Identification and study of genes involved in the positive and negative control of cell migration, proliferation, differentiation and death (apoptosis).*

A.2 Use of high-tech methods for the selective targeting of tumour cells

- *Identification of new specific cancer cell markers which may be used by new methods as therapeutic targets.*

A.3 Predisposition to, early diagnosis of and early detection of metastases using new technologies and development of new molecular reagents

- *Use of biochips to determine the genetic profile of a normal cell and a cancer cell, and the profile of cancer cells at various stages of development of the tumour.*
- *Development of new diagnostic tests and procedures to identify specific genetic changes from which it is possible to evaluate a person's cancer risk.*
- *Development of sophisticated surgical pathology techniques to help improve the early detection of cancers.*

A.4 Computerisation of data collection

- *Development of data bank systems with software which is user-friendly and compatible with similar systems in the other EU countries, enabling data to be collected centrally at European level.*
- *Refinement of bioinformatics tools for the collection and analysis of genome data and the integration of genome and phenotype data.*

B. Cardiovascular disease

Cardiovascular disease is now the leading cause of death in the developed world, ahead of cancer. Studies conducted as part of the WHO MONICA Project (Multinational Monitoring of Trends and Determinants in Cardiovascular Disease) suggest that 5.52 million people (45.6% of all deaths) die as a result of a cardiovascular disease in the developed world.

A significant and noteworthy factor here is that often it is middle-aged individuals, i.e. those at the peak of their productivity, who are seriously affected by these diseases, and that this creates a major problem for society and the economy.

The BIOSAN Programme specifically targets two central cardiovascular pathologies, myocardial infarction and cardiac insufficiency, and seeks to improve the prevention and treatment of these two pathologies.

Key actions:

B.1 Analysis of the cellular and molecular mechanisms implicated inter alia in diseases of the heart and vascular system, and including cardiovascular inflammation

- *Study of cell-cell interactions (e.g. blood cells-vascular wall). Characterisation of the role of certain molecules (growth factors, cytokines, adhesion molecules, components of the extracellular matrix, lipids, coagulation factors) and their signal transduction mechanisms in the development of cardiovascular disease. Differential expression of surface antigens, receptors and ion channels in normal and pathological vascular cells.*
- *Proliferation of normal and pathological vascular and cardiac cells. Study of repair mechanisms after injury (e.g. proteinases, free radicals, antioxidants) and of other regulatory mechanisms which may prevent injury or speed up the repair of vascular lesions.*
- *Inflammatory mechanism and cardiovascular disease. Biological mechanisms of arterogenesis and thrombosis.*

B.2 Research into the understanding of the genetic basis of cardiovascular disease and myocardial infarction

- *Identification of genes implicated in the development of cardiovascular disease.*
- *Genetic predisposition, risk factors, interaction with non-genetic risk factors.*

B.3 Clinical evaluation of new invasive or non-invasive imaging methods for the early diagnosis of cardiovascular disease

B.4 Evaluation of new approaches (e.g. physical training) to the treatment of patients with cardiac insufficiency, and cost/benefit assessment compared with conventional treatments

C. Novel strategies for immune intervention

The natural role of the immune system is bioremediation inside the organism. It protects against the challenge of agents which invade the organism and may cause disease. To keep the organism 'clean' the immune system has a range of effector mechanisms designed to neutralise invading agents. It is well known by the general public that the immune system protects against infectious diseases caused by viruses or bacteria. By immunising, the immune system can be trained to clear pathogens more efficiently. Today preventive applications of immunisations are still essentially limited to viruses and bacteria.

The immune system also plays an important role in clearing cell debris, tumour cells, transplants, allergens, toxins, etc. It is clear by now that the natural specificity of the immune response can be modulated with respect to some of these targets or specifically directed against these and many other targets. This will vastly expand preventive and therapeutic applications of immune interventions.

These may include, for instance, therapeutic or preventive vaccination against infectious agents (viruses or bacteria) that cause diseases where such agents have not or until recently not been suspected, immune intervention against tumour cells, immune intervention to modulate mediators of the immune system itself, etc. Exciting synergies with cancer and cardiovascular research may also develop from a number of these applications.

However, for most of these applications of immunology to be effective, our understanding of the immune system must be improved and experimental model systems must be developed. The development of many of these new applications of immune intervention includes fundamental research and *in vivo* studies.

The BIOSAN Programme targets the

- **development of novel applications and strategies for immune intervention**
- **exploitation synergies between cancer research and cardiovascular research and immunology**
- **basic and applied research towards the development of the immunological basis for the above two areas of applications**

Key actions:

- C1. Development of model systems for immune intervention***
- C2. Mechanisms of immune suppression (e.g. of tumour cells)***
- C3. Basic research for the development of novel immune intervention strategies, e.g. modulation of the Th1/Th2 balance***
- C4. Identification and development of novel antigens for immune intervention and immune modulation***
- C5. Vaccination against small molecules that cause health hazards such as environmental hazards (e.g. carcinogens, toxins etc.), behavioural hazards (drugs of abuse, smoking), endogenous health hazards (e.g. cholesterol, cytokines, hormones)***
- C6. Therapeutic vaccination against cancer cells and other immune interventions against cancer (e.g. immunisation against neovascularisation)***
- C7. Mechanisms of allergy and immune intervention against allergies***

D. 'Medical Aspects of Ageing (PROVIE)'

In Luxembourg the number of people aged 65 and over rose from around 50 000 to 61 000 between 1991 and 2001, and the number of those aged 80 and over rose from under 12 000 to about 13 500, equivalent to an increase of over 20% and just under 13% for these two age groups. Quality of life for the population as a whole falls off sharply in the 80+ age group due to physical disabilities and impaired cognitive and neurological function. The resulting need for care of elderly patients creates numerous problems of a family, social, financial and psychological nature.

Comment [k1]:

Comment [k2]:

At the same time, epidemiological data on the diseases of old age, both physical and mental, remain imprecise. The medical diagnosis of specific geriatric disorders often lumps everything together ('senile syndrome'); and associated problems such as sleep disorder, depression and pain are not analysed separately. Doses for specific treatments, set for other age groups, are often not suitable for older patients; elderly patients are also often excluded from medical studies because of their multimorbid physical and mental condition, because of a weaker capacity for cooperation and a poor tolerance of drugs. There are, moreover, not enough professionals trained in the care of older patients and their families.

The aim of this specific research area is to study the epidemiological, psychosocial and biological aspects of the neurodegenerative diseases of old age in Luxembourg and view them against the broader European canvas. In line with the EU research programme on 'medical and social challenges posed by an ageing population and the disabilities associated with old age' (Official Journal of 15 November 2000), the approach taken is a holistic one, i.e. multidisciplinary and multidimensional. Priority will be given to projects which are multidisciplinary and interactive, involving players from different specialist backgrounds.

Objectives:

- To improve the skills of the biomedical community in Luxembourg and the transfer of knowledge concerning pathologies linked to ageing of the brain
- To correlate medical, epidemiological, psychosocial and biological aspects
- To improve the prevention of cerebrovascular accidents (strokes)
- To acquire innovative detection methods for neurodegenerative diseases, depression, sleep disorders and chronic pain in the elderly
- To devise new specific treatment strategies for the above pathologies
- To improve the care of the patients and their families
- To develop new therapies

The aim, in pursuing these objectives, is to attain an internationally recognised level of medical and scientific competence and to ensure that work done under this Programme meshes with other national and international projects. Measures to support research forums or cycles of specialist seminars may be organised and funded under the Programme.

The BIOSAN Programme specifically targets pathologies linked to the ageing of the nervous system, and more especially the brain. The approach to pathophysiology is a cross-cutting one, combining methods used in basic and clinical or applied research.

Key actions:

D.1. Basic research and technology transfer

- Cell and molecular pathophysiology of the neural and glial cell
- Age-related changes in cerebral vasoreactivity
- New knowledge concerning mental disorders, chronic pain, sleep and day-time somnolence in the elderly, in both elderly patients who are healthy and those with specific pathologies (Alzheimer's, Parkinson's), and transfer of this knowledge to appropriate therapies or treatments
- Examination of biological conditions associated with the processes of cerebral ageing

D.2. Early diagnosis and definition of follow-up monitoring aids

- Risk or protection factors, primary and secondary prevention
- Medical imaging, biomarkers for medical diagnostics
- Refinement of medical diagnosis, of co-morbidity (sleep, pain, mental and vascular problems); multidisciplinary approach including psychosocial aspects
- Promotion of the assessment of symptoms and biological parameters in patients with minimal pathology, to collect the necessary elements which will allow a diagnosis of pathophysiology, still uncertain for the moment, to be conclusively made for the future.

Comment [RB3]: Fruste = ????

D.3. Clinical and epidemiological aspects

- Revision of the standard clinical definitions used by physicians and other health professionals, bringing them into line with existing international nomenclatures, and improvement of the nomenclature lists for medical, nursing and welfare acts to allow comprehensive and detailed records to be kept of the acts performed on elderly patients or in their care institutions; proposal of methods (with assessment of their financial cost) which would make these new definitions and nomenclatures an integral part of routine operations in health care establishments (e.g. training, support and supervision, payment for statistical record-keeping)
- Evaluation of drug consumption, improvement of non-medical care, rehabilitation
- Quality of life and 'coping', support for the family, identification of social and family criteria which allow persons with dementia to remain at home as long as possible
- Investigation of the treatment given to patients with neurological and mental disorders (e.g. as inpatients and outpatients; drugs taken; welfare assistance given)
- Longitudinal monitoring of the population using clearly defined diagnostic criteria; statistical processing of the data: development of standard methods for extracting the useful data, with procedure for comparing data from different sources, creation of disease registers (real or virtual) for essential target pathologies (e.g. Alzheimer's, stroke, Parkinson's), keeping personal data confidential
- Evaluation of standard instruments for measuring the degree of dependence/disability and quality of life of the elderly
- Search for correlations between biological, medical and social conditions associated with the processes of cerebral ageing: identification of factors which may foster or prevent the processes of cerebral ageing, so that effective programmes can be put in place to prevent these processes

- Studies of the cost of the various forms of care for patients with neurological and mental problems, according to the type of care or establishment, of the burden placed on families by a person with an age-related neurological or mental illness;
Time modelling of the health and social cost of neurological and mental illness in the elderly in Luxembourg;
Evaluation of alternative forms of care for elderly patients with neurological or mental problems, including not just the cost assessment but also a quality-of-life assessment. The study of alternatives must pave the way for new policies or new pilot projects testing the feasibility of an alternative approach.

For most of the research topics in this specific research area, cooperation between the research sector on the one hand and the health sector on the other hand will enable projects to have a greater impact, through specific involvement of the appropriate ministries or government departments.

Comment [k4]:

Comment [k5]:

E. Expression library technology for functional and topographic targeting of complex biological systems

Library technologies are powerful tools in basic research to study protein-protein interactions and functions. Competence will be developed in this important technology which has a very wide range of applications in life sciences. The programme will help to fill a technology gap both in basic and applied biomedical research. The establishment of this technology in Luxembourg is highly attractive for companies wishing to acquire the technology or to out-source library screening to research partners in their immediate neighbourhood. The technology is highly valued for its potential to identify new therapeutic targets, for identifying and developing molecules for new diagnostic approaches and identifying new innovative lead compounds for drug and vaccine development. It will help to establish Luxembourg as a reliable partner in biotechnology. The programme will foster close collaboration in a national and regional partnership to make full use of synergies resulting from ongoing projects and existing expertise.

To be eligible under this programme, applications in this area of technology must be relevant to key actions A, B, C or D described above.

Key actions:

E1. Identification of receptors and ligands, e.g.

- *Identification of cell surface receptors (e.g. of physiological ligands or pathogens)*
- *Identification of small molecular substitute ligands*

E2. Library-library screening, e.g.

- *Development of model libraries that can be reacted with each other and rely on independent ('orthogonal') replication systems*
- *Screening of random phage libraries against cDNA expression libraries of increasing complexity*
- *Screening of more or less limited cDNA expression libraries against each other*

E3. In vivo targeting

- *Vaccine delivery to specific immune competent cells such as dendritic cells*
- *Drug delivery to tumour cells*
- *Specific targeting of compartments (e.g. inflammatory sites, blood brain barrier, joints, transcutaneous delivery, transmucosal delivery, etc.)*

E4. Applications of expression libraries to the analysis of allergenic epitopes in allergic diseases, e.g.

- *Definition of allergens and autoantigens and their epitopes with random phage libraries or gene-specific libraries*
- *Analysis of the allergic profile of novel dietary or respiratory allergens*
- *Use of gene-specific libraries to analyse the antibody profile against cloned auto-antigens in auto-immune diseases*

F. Epidemiology

Analytical epidemiology, which provides the basis of research into and a better understanding of endogenous and exogenous factors in the pathology of cancer and cardiovascular disease and – in a second phase of the BIOSAN Programme – of the diseases of old age, is not very developed in Luxembourg.

The study of endogenous factors, more commonly called ‘genetic epidemiology’, allows us to analyse cohorts of subjects and from them define a group of risk factors. The WHO recommends this type of analysis in the conduct of its health programmes.

Analysis of endogenous factors such as nutrition or environmental influences is also becoming more and more indispensable in the clinical study of these pathologies.

The expertise to be developed in analytical epidemiology will be of infinitely greater value both for the study of cancer and cardiovascular disease (dietary habits, smoking, other toxic substances linked to environmental problems, etc.).

Key actions:

F.1 Identification of risk factors for exposed populations; study of the role of social and ethnic factors and of the interaction between genetic and environmental factors; risk prevention and management

F.2 Study of the relationships between hypertension, cardiovascular disease and genetic, environmental and ‘lifestyle’ predispositions

F.3 Development of measuring aids in genetic epidemiology and link with population change

F.4 Research into new multifactorial systems for monitoring health

F.6 Assessment of the socioeconomic impact of health initiatives and measurement of their performance, taking into account socioeconomic changes and the development of health information systems

G. Intelligent IT environments in the health field

Information technology plays an increasingly vital part in all areas of health care (public health, social security, medical care and research).

Information technology is there wherever data are manipulated, processed and exchanged.

The present programme envisages two areas of key action in which skills are to be built up:

- Bioinformatics: to create the capability to manage the manipulation and exploitation of data produced by use of new technologies such as biochips or expression libraries
- Telemetry or 'home monitoring': in the context of surveillance and domiciliary treatment, use of 'intelligent instrumentation' which links the patient to a care and diagnostic centre via the national communication system HealthNet.

Key actions:

G.1. Creation of skills in the field of bioinformatics, to be able to manage the complexity of data produced by new analytical procedures (such as biochips or 'expression libraries')

G.2. Creation of online healthcare skills ('home monitoring') using HealthNet, encouraging the development of telemedicine and biotelemetry

3) Budget breakdown of the BIOSAN programme

	Budget for the priority areas A-C and related areas E-G 1 st call : 2001	Additional budget for the implementation of priority area D (PROVIE) and related areas E-G 2 nd call : 2003	Total Budget BIOSAN Total per year	Changes in comparison with the current contract between the State and the FNR Variations
2001	1.000.000		1.000.000	+/- 0
2002	1.500.000		1.500.000	+/- 0
2003	500.000	500.000	1.000.000	+/- 0
2004	1.250.000	1.000.000	2.250.000	+ 750.000
2005	1.250.000	750.000	2.000.000	+ 1.000.000
2006	500.000	250.000	750.000	+ 750.000
Total	EUR 6.000.000	EUR 2.500.000	EUR 8.500.000	+ 2.500.000

4) Criteria to be met by the BIOSAN programme

Comment [RB6]: Critères à respecter par les propositions de projets

The BIOSAN Programme will seek to encourage interaction between basic, clinical and technological research on a multidisciplinary basis and with an eye to the likely socioeconomic effects. The programme will look for proposals (for research projects) involving at least one Luxembourg research team.

The Programme will draw on skills represented in the field of life sciences and will ensure that several laboratories or bodies based in the Grand Duchy are involved in each project.

The Programme envisages targeted multidisciplinary key actions which will require the various players involved in the Programme to work together.

Proposals must be consistent with the key actions listed; a proposal may, however, cover more than one key action.

The Programme will look for generic activities designed to build up new knowledge bases in the field of its key actions.

The Programme will endeavour to favour the industrial development of biotechnology in the Grand Duchy.

In addition to the key actions and generic activities, the Programme also envisages activities such as infrastructure support, the dissemination and exploitation of results, and training.

The criteria for assessing and selecting proposals may be summarised as follows:

- *High-quality scientific, clinical and technological approach together with an innovation strategy*
- *Projects submitted must have a mobilising effect*
- *Skills and generic expertise must be built up from specific projects*
- *Objectives must be clear, realistic and quantifiable over time*
- *Budgets must be realistic and consistent with the objectives set*

Specific criteria for the 2003 call (PROVIE):

Each project submitted must:

- a. meet the seven criteria listed in the Annex
- b. make sensible use of the skills and equipment available in Luxembourg and in the international collaborative network
- c. mobilise a scientific grouping in a multidisciplinary, multi-team and integrated approach; consequently each project should cover at least two sections of the programme being related to the thematic priority of “Medical Aspects of Ageing (PROVIE)” (priority areas D and related areas E-G)
- d. plan to coordinate its work with other national projects and cooperate with international projects
- e. plan adequate support and supervision for the research workers involved
- f. provide proof of the requisite statutory and ethical authorisations.

Comment [RB7]: Indiqués en annexe (mettre la liste standard en annexe) et enlever l'énumération ici

NB: The National Research Fund (FNR) will only fund research projects and not work or studies routinely required of the bodies concerned.

General FNR Criteria used to select research projects

1. Scientific Quality

- creativity
- novelty and innovation
- scientific methods used
- production of new expertise
- coherence of the project
- project's ability to encourage interdisciplinary working
- projects must aim to achieve an internationally recognized level of expertise

2. Socio-economic value

3. Cost-effectiveness

4. Consistency with the objectives and priorities set out in the extension “Medical aspects of ageing (PROVIE)” (research area D and related areas E-G) of the BIOSAN programme

5. Realistic nature of project within the Luxembourg context

- realistic in terms of financial resources
- on-the-spot scientific/technological potential (are there enough skilled human resources which can be deployed within the time constraints of the project?)
- support capability for the beneficiary establishments involved

6. Mobilisation of national resources:

- cooperation by multiple research establishments based in Luxembourg
- involvement of multiple establishments, businesses or industrial firms and groups based in Luxembourg which are potential users of the project's results

7. Budget breakdown

The budget for a project must show a balanced breakdown between the :

- acquisition of expertise
- actual research work
- dissemination and exploitation of the research findings
- other supporting measures