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Biotechnology and applied genomics for health: initiatives of the European Union☆

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1. Introduction

The sequencing of the human genome and many other genomes heralds a new age in biology and on medicine, offering unprecedented opportunities to improve human health and to stimulate industrial and economic activity. Dramatic progresses are expected in the coming years on areas such as drug discovery, development of new diagnostics, development and testing of new preventive and therapeutic tools, in particular stem cell therapies.

The European Union has been funding research in this area for over a decade. This support has led to the establishment of collaborative links between European groups, particularly between academia and industry. This article summarises the main contributions from the 'Cell Factory' Key Action in the Fifth Framework Programme for Research, Technological Development and Demonstration (RTD) of the European Union (1998–2002) [2] and the current initiatives for the Sixth Framework Programme (2002–2006) [3]. These initiatives are aimed at promoting translational research on Biotechnology and Applied Genomics for health, that is to say, to bring basic, fundamental knowledge to an application stage to enable real, consistent and co-ordinated progress at European level in medicine, competitiveness and quality of life.

The Cell Factory is one of the six Key Actions of the Quality of Life and Management of Living Resources Programme of the Fifth Framework Programme (1998–2002). The Cell Factory has a budget of €400 million and its objective is to support research activities that aim at the integration of innovative research and technologies with their exploitation by industry and/or other socio-economic entities in the fields of health, environment, agro-industry, agri-food and high value added chemicals. The Cell Factory promotes an environment in which scientific results can be rapidly exploited and transformed into products and processes of interest to society. This approach is facilitated through integrating the whole innovation process, from advanced fundamental research, through technological development to practical demonstration. Elsewhere in this article a summary of the most relevant research projects and activities are described.

The Specific RTD Programme 'Integrating and Strengthening the European Research Area' of the Sixth Framework Programme (2002–2006) [4], addresses, again, these challenges in its First Priority: 'Life Sciences Genomics and Biotechnology for Health' which has a budget of €2255 million. This Priority focuses on the integration of post-genomic research into the more established biomedical and biotechnological approaches. It also aims to facilitate the integration of research capacities available in, both, the public and private sectors across Europe and to increase coherence, synergism and to achieve critical mass. Research activities to be supported under this Priority will address research through an integrated multidisciplinary approach, which promotes a strong interaction between technologies and scientific disciplines. This integrated multidisciplinary approach is essential in this Theme for translating genome data into practical applications for human health. The second part of the article addresses the current development in the preparation of the Sixth Framework Programme and, in particular, the activities foreseen in the area: Applications of knowledge and technologies in the field of genomics and biotechnology for health.

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2. Fifth framework programme: Key Action 'Cell Factory' [5,6]

An important element of the research activities supported within this Key Action addresses the field of human health and therapeutic interventions and may be summarised in Table 1.

A clear focus on a series of specific diseases and health problems can be seen, ranging from microbial resistance, cancer and neurodegenerative disorders, to graft implants and organ transplantation. Further details may be found in specific Commission publications [1,2].

3. Therapeutic substances

In this area, a distinction can be made between those projects directly addressing the identification of potential drug targets and development of new therapeutic biomolecules on one hand and those dealing with the design or improvement of production systems for these biomolecules. In the first group, specific medical needs, such as anti-infectives and cancer therapeutics are addressed by several projects. These aim to identify and characterise new therapeutic targets, such as receptors and molecular cascades involved in the development of disease (oncogenesis, angiogenesis, etc.), or to develop new lead compounds (novel anti-microbial, anti-protozoal and anti-viral substances), and antineoplastic agents (glycosaminoglycans and vaccines). Other disorders covered include rare metabolic diseases (alpha-mannosidosis), neurodegenerative disorders (Alzheimer's, Parkinson's disease), urinary incontinence and body dehydration.

Table 1
Research activities of Key Action 'Cell Factory' addressing health

Area	No. of projects	EC contribution € (million)
Therapeutic substances		
New compounds (incl. Biol. production)	31	62
New targets	18	36
Delivery systems	5	8
Drug intermediates	2	4
Subtotal	56	110
Therapeutic strategies		
Gene therapy	11	22
Stem cells therapies	9	20
Immunotherapy	11	21
Tissue engineering	5	7
Other therapeutic strategies	5	10
Subtotal	41	80
In vitro testing	6	10
Development of new diagnostics	14	23
Total	117	223

Specific topics that fill certain gaps in the health sciences area of the Key Action 'Cell Factory', include a project focusing on bone repair. This innovative undertaking aims to design matrix molecules for hard tissue repair and bio-mineralisation and although its remit is primarily dental treatment, it nevertheless opens up a vast field of potential applications for related disorders including arthritis, bone replacement and orthopaedic surgery. A specialised SME in this consortium deals with product stability and toxicity testing.

Other projects that enlarge the scope of the Cell Factory health sciences portfolio include projects that respectively aim to develop new therapeutics for autoimmune disorders using *Myasthenia gravis* as model disease and to employ the properties of Heme oxygenase to treat chronic inflammation.

A very innovative and ambitious project searches to identify compounds that interact with prions and hence reduce the infectivity of Transmissible Spongiform Encephalopathy (TSE). This examines potential treatments in the field of TSEs, including peptides and an SME in the consortium specialises in the synthesis of these peptides.

Other examples include:

- a Demonstration project aiming at the development of universal cell-free cancer vaccines based on 'exosomes', which also includes clinical trials on metastatic patients,
- a project aiming at the identification of inhibitors of toxin–antitoxin-complex formation in microbes, as potential new antibiotics. The industrial partner involved is a well established company, active in the field of antimicrobial development.

The area of new delivery systems for biomolecules makes use of micro-organisms (e.g. non-pathogenic lactic acid bacteria or clostridium species) and viruses (e.g. parvoviruses) to deliver vaccines or therapeutic substances. In another case, new biodegradable particles will be developed for releasing highly potent pharmaceutical compounds in a controlled manner into the central nervous system for the treatment of brain cancers and neurodegenerative disorders (Parkinson's and Huntingdon's Disease).

4. Therapeutic strategies

In this area, 39 projects utilise the important potential of 'cell factories' as new therapeutic tools, for gene and cell therapy, immunotherapy, or else use these instruments as improved delivery systems for therapeutic interventions.

4.1. Gene therapy

The development of vectors is a common issue of many projects in gene therapy, with most of these aiming to develop new generations of viral vectors for gene therapy of the haemopoietic system, neurodegenerative diseases, liver and brain cancer, or to treat neoplastic and viral disorders by immunotherapeutic approaches. Some address completely novel therapeutic approaches such as the in-vivo repair of gene mutations, or transfer genes so as to express therapeutic substances, using 'multicistronic' viral and non-viral vectors for cancer, retinopathies and arteriosclerosis.

In this field, the objectives of the 11 projects selected for funding comprise the treatment and prevention of cancer, polycystic kidney disease and Parkinson's disease. Two Demonstration Projects are included, which respectively aim to develop standard operating procedures for the use of non-viral gene therapies to treat cancer and to enhance retrovirus production for the treatment of dystrophic epidermolysis bullosa. Finally, two research and development projects aim to design more efficient vector systems as the basis for safer strategies of gene transfer.

4.2. Cell therapy

In the cell therapy field, several projects use cells to treat chronic and degenerative disorders such as osteochondrodysplasias, Parkinson's disease or multiple sclerosis. Another focus is on the transfer of expertise in cord blood technologies to clinical practice.

Several projects aim specifically to treat neoplastic disorders by the identification of novel therapeutic interventions. Some aim to improve engraftment methods and to prevent life-threatening post-transplant complications (e.g. Graft-versus-Host disease) in haemopoietic disorders. The idea is to design clinical protocols for the ex vivo expansion of umbilical cord blood stem cells, thereby improving clinical outcomes, as well as make a better prediction of this outcome, based on genetic and clinical risk assessment derived from in vitro biotechnology. One particular project aims to cure several genetic diseases based on therapeutic gene transfer into autologous haemopoietic stem cells. The main focus is the development of optimised viral vectors for gene transfer protocols and among the members of the consortium is the hospital, which is credited with the first successful use of gene therapy in two cases of genetic haemophilia.

Other issues addressed in this area are the in vitro maintenance of organ-specific stem cells and the creation of bioartificial organs (e.g. liver) and tissue grafts (e.g. osteochondral defects).

4.3. Immunotherapy

Immunotherapy-related projects collectively aim to produce vaccines for cancer and allergies. Of these, one particularly innovative project focuses on the generation of antibodies against new blood vessels so as to treat angiogenesis-related pathologies. Two additional projects aim to enhance immunologically mediated tumour rejection based on dendritic cell and glycoprotein vaccination. Two others aim to develop novel therapeutic interventions for human autoimmune diseases and allergies via the development of vaccination strategies.

Two remaining projects aim to develop new pharmaceutical products based on chemical signalling pathways in the pathogenesis of rare pulmonary diseases.

4.4. Tissue engineering

Graft development is tackled by two tissue engineering-related projects, one focusing on the design and testing of a sophisticated nerve repairing graft and the other redressing the cellular production of human recombinant collagens and growth factors and their use in vascular grafts. The three remaining projects combine stem cell techniques with those related to tissue engineering. One of them is the first EU-funded project that uses existing human embryonic stem cell lines and aims to develop bioengineered pancreatic islet microorgans for insulin replacement therapy. The field of hard tissue repair is reinforced by a project, which applies genetically engineered mesenchymal adult stem cells to create cartilage implants. The regeneration of lung epithelium is addressed by another project, which focuses on the design of genetically engineered stem/progenitor cells transplants, based on a novel gene transfer technology.

5. In vitro alternatives to animal testing

All projects in this area are expected to increase and accelerate the discovery of novel therapeutic agents. They will particularly reinforce pre-normative research, which is linked to Directive 86/609 on the protection of animals used for experimental and other scientific purposes.

The first project has the aim to develop and validate a method based on the human fever reaction to replace the rabbit pyrogen test and the *Limulus amoebocyte lysate* (LAL) test. It is expected that this method will be introduced into the European Pharmacopoeia. The objective of the second project is to exploit recent advances in immunology to develop *in vitro* model systems of the human immune response for the prediction of the capacity of recombinant proteins to induce allergic reactions in humans.

The aim of the third project is to develop a cell culture system based on a chicken cell line to analyse vertebrate gene function as an animal-free substitute to mouse transgenesis. This will enable small laboratories with limited access to animal facilities to analyse proteins of interest by genetic methods.

6. Development of new diagnostics

Projects in this area aim at the early detection and diagnosis of a wide range of diseases, including neurological, metabolic and neoplastic disorders. Of these, one project uses genetic analysis procedures based on the DNA mimic, Peptide Nucleic Acid (PNA) as probes for mutations in capillary electrophoresis to detect gene mutations in cystic fibrosis, whereas another large consortium, consisting of 21 of the most experienced laboratories working in Alzheimer's disease, will develop standardised diagnostic screening strategies combining genetic, patho-physiological and biomarker information. Other projects deal with Creutzfeld-Jacob disease, osteoporosis, vascular pathologies and vitamin B12 deficiency.

7. SMEs (Small and Medium-Sized Enterprises)[1] and Innovation

European research efforts in responding to the challenge of developing new therapeutic interventions for the 21st Century depend largely on a better integration of life sciences research and technological activities carried out both by industry and academic institutions in collaboration with other socio-economic entities in the various different fields. Collectively, these activities are widely regarded as enabling technologies, which offer a broad spectrum of applications to meet societal needs as well as being an important source of economic growth, through the creation of large numbers of skilled jobs [7].

Empirical estimates at this time show that by the year 2010, there will be a total world market (excluding agriculture) of over €2000 billion in those sectors with a strong basis in biotechnology. The pharmaceutical industry is a strong integral part in this sector, for which the direct and indirect market potential has been estimated to reach €818 billion by this year [7]. On its own, the European biotechnology market for year 2005 is expected to exceed €100 billion.

Indeed, there are signs of significant growth of the life sciences bioindustry in Europe every year. For example, while the number of biotechnology companies appears to have levelled out (8% growth from year 2000 to 2001), the level of employment in biotechnology companies has shown a significant increase (of 29% over the same period) [8]. There has also been a rapid expansion of start-up biotechnology companies in Europe in the recent past, with greater numbers now in Europe (1570) than in the US (1273) [7]. In particular, the number of dedicated bio-pharmaceutical companies rose from 35% to over 50% of the total number of new firms, between 1995 and 2000. This is mainly due to the reinforcement of the pharmaceutical sector, based on using platform technologies such as combinatorial chemistry and bio-informatics (genomics, proteomics, metabolomics, etc.) to speed up the drug development process [9]. However, the growth of these companies and their revenues still lag behind those of their USA counterparts.

The Key Action 'Cell Factory' of the Fifth Framework Programme, has devoted particular attention to the exploitation of research results so as to encourage the further development of established bio-industries and to start-up new biotechnology companies. A prerequisite of any project to receive funding was the capacity to link the ability to discover to the ability to produce and examples of this in action include:

7.1. Encouragement of industrial companies to become partners in the fifth framework programme projects

(1) Pre-requisites for the funding of share-cost actions have been a firm commitment to the transfer of knowledge along with convincing strategies for the exploitation of research results. This enabled the Commission to achieve 79% industrial penetration[2] and 18% industrial participation[3] in all projects funded by 'Cell Factory'. There are 282 industrial participants, ranging from SMEs (53%) to large-scale industrial corporations (47%). Over 15% of the EC contribution to Fifth Framework Programme shared-cost research projects was allocated to industrial partners (€55.5 million) of which half was attributed to SMEs.

[1] Industrial penetration = No. of projects with at least one industrial partner/Total no. of projects.

[2] Industrial participation = No. of industrial partners/Total no. of partners.

[3] An SME in Framework Programme 5 (FP5) is an enterprise which fulfils the following three criteria: (1) has fewer than 250 employees; (2) has either, (a) an annual turnover not exceeding €40 million, or (b) an annual balance-sheet total not exceeding €27 million; (3) is independent, i.e., is not owned by 25% or more by one or more organisations which are not an SME (except public investment corporations, venture capital companies and funds and institutional investors).

(2) In the Key Action 'Cell Factory', a total of 52 projects specifically involving SMEs have been funded with a total budget of €8.7 million.

(3) Biotechnology companies have been encouraged to participate in training activities for young researchers under the Marie Curie Host fellowship scheme. More than 50% of the host institutions participating in projects funded by Key Action 'Cell Factory' are biotechnology companies (e.g. Rhône-Poulenc-Rorer R&D, Glaxo R&D, Pharmacia AG, Novo Nordisk).

7.2. Promoting dialogue and fostering competitiveness

A key objective of Key Action 'Cell Factory' has been to stimulate dialogue between the main actors in the drug development field in order to identify existing bottlenecks at the interface between the nascent medical biotechnologies and clinical practice. A second objective has been to explore potential opportunities to strengthen the competitiveness of the European bio-medical development sector and the health care industry. Several events have been organised by the Key Action 'Cell Factory' including:

Workshop: 'Entrepreneurship: Networking of Biovalleys in Europe', Brussels, May 27, 1999 (http://www.europa.eu.int/comm/research/fp5/eag-qol-entr.html)
Workshop: 'New Safe Medicines Faster', Brussels, March 15–16, 2000
Conference: 'From Medical Biotechnology to Clinical Practice', Brussels, June 8–9, 2000,
Workshop: 'Industrial Platforms in Life Sciences', Brussels, October 31, 2000
Congress: 'New Safe Medicines Faster', Stockholm, October 20–23, 2002 (http://www.eufeps.org)

The Key Action ' Cell Factory' has also contributed to the drafting of EC regulations affecting the biopharmaceutical industry, giving rise to specific policies in the field of drug development and testing:

Second Council Directie 75319EEC of 20 May 1975 on the approximation of proisions laid down by Law, Regulation or Administratie Action relating to proprietary medicinal products
Regulation EC No. 1412000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products
Directie 9844EC of the European Parliament and of the Council of 6 July 1998 on the legal protection of biotechnological inentions
Council Directie 9342EEC of 14 June 1993 concerning medical deices
Directie 9879EC of the European Parliament and of the Council of 27 October 1998 on in itro diagnostic medical deices
Council Directie 67548EEC of 27 June 1967 on the approximation of laws, regulations and administratie proisions relating to the classification, packaging and labelling of dangerous substances
Council Directie 76768EEC of 27 July 1976 on the approximation of the laws of the Member States relating to cosmetic products
Council Directie 86609EEC of 24 Noember 1986 on the approximation of laws, regulations and administratie proisions of the Member States regarding the protection of animals used for experimental and other scientific purposes
Proposal for regulatory actions on Paediatric medicinal products

In order to maintain this momentum, the Commission has determined that 15% of the budget allocation shall be set aside for SME partners in all thematic priorities for the Sixth Framework Programme. This requirement was confirmed in the political objectives set up by European Council Summits in:

Lisbon 2000, which set the target of '...making the EU the most competitive and dynamic knowledge-based economy in the world by 2010', and
Barcelona 2002, which set the goal of reaching 3% of GDP in R&D investment in Europe, with a particular increase of business funding from current figures to two-thirds of total R&D investment.

This represents the main challenge for the thematic area 'Applied Genomics and Biotechnologies for Health' which aims to foster competitiveness in the European biotechnology industry.

8. The sixth framework programme

Life Sciences and Biotechnology are therefore widely and justifiably regarded as one of the most promising technologies for the coming decades and may be applied for a wide range of purposes for private and public benefits. On the basis of recent technological breakthroughs, a continuous stream of new applications may be expected. One of Europe's main strengths in this regard is its strong science base, which has the potential to redress the imbalance with regard to the US as

outlined above by harnessing those efforts that are ongoing to open up new possibilities through multidisciplinary research [7]. Three main pillars for action in biotechnology are envisaged: a reinforcement of the knowledge basis by encouraging a freer and more efficient dialogue and exchange of scientific information and data between research institutions and other actors in the field, a closer networking of European biotechnology communities to create a platform for future research activities and to involve policy-makers and other decision-makers into the debate so as to anticipate emerging needs and proactively adapt policies.

The Sixth Framework Programme of the European Community for Research, Technological Development and Demonstration Activities [3] takes into account these realities facing Europe in the future and accordingly adopts a novel approach. This involves assembling genuine critical masses of resources, a better co-ordination of national research efforts and the diversification of support activities in key areas such as the mobility of researchers, research infrastructures and science and society issues. With a budget of €17.5 billion (€1.23 billion for European Atomic Energy Research and €16.27 billion for research activities of the European Community), its overall objective is the creation of a European Research Area (ERA). This aims at scientific excellence, improved competitiveness and innovation through greater co-operation and complementarity between all relevant actors, in order to transform the European Union into the most dynamic and competitive knowledge-based economy in the world.

To realise this, three main avenues of activity of European Community research with corresponding budgets (million €) have been identified and further details can be found at http://www.europa.eu.int/comm/research/fp6/index_en.html.

9. Life sciences, genomics and biotechnology for health

The main provisions of this first thematic Priority, which deals with biomedical and health-related research, are set out as follows:

Priority: 'Life Sciences, Genomics and Biotechnology for Health'

i) Advanced genomics and its applications for health (€1100 million)
   a) Fundamental knowledge and basic tools for functional genomics in all organisms
      - Gene expression and proteomics
      - Structural genomics
      - Comparative genomics and population genetics
      - Bioinformatics
      - Multidisciplinary functional genomics approaches to basic biological processes
   b) Application of knowledge and technologies in the field of genomics and biotechnology for health
      - Technological platforms for the development in the field of new diagnostic, prevention and therapeutic tools
      - Rational and accelerated development of new, safer, more effective drugs including pharmcogenomics approaches
      - Development of new diagnostics
      - Development of new in vitro tests to replace animal experimentation
      - Development and testing of new preventive and therapeutic tools, such as somatic gene and cell therapies (in particular stem cell therapies[4], for example those on neurological and neuromuscular disorders) and immunotherapies
      - Innovative research in post-genomics, which has high potential for application
ii) Combating major diseases (€1155 million)
   a) Application-orientated genomic approaches to medical knowledge and technologies
      - Combating, cardiovascular disease, diabetes and rare diseases
      - Combating resistance to antibiotics and other drugs
      - Studying the brain and combating diseases of the nervous system
      - Studying human development and the ageing process
   b) Combating cancer
   c) Confronting the major communicable diseases linked to poverty

This first theme will focus on integrating post-genomic research into the more established biomedical and biotechnological approaches and will facilitate the integration of research capacities (both public and private) across Europe to increase coherence and achieve critical mass. This thematic priority area will stimulate and sustain multidisciplinary basic research to exploit the full potential of genome information to

[4] Pending the establishment of detailed implementing provisions, research activities involving the use of human embryos and human embryonic stem cells will not be funded, with the exception of the study of banked or isolated human embryonic stem cells in culture. The detailed implementing provisions should be in place by the end of 2003.

underpin applications to human health. The instruments employed comprise traditional actions such as specific targeted research projects, coordination actions and specific support actions already common in the Fifth Framework Programme. Two additional new instruments are envisaged: Integrated Projects and Networks of Excellence.

Integrated project

Integrated projects are designed to give increased impetus to the Community's competitiveness or to address major societal needs by mobilising a critical mass of research and technological development resources and competence. Each integrated project will be assigned clearly defined scientific and technological objectives and should be directed at obtaining specific results applicable in terms of, for instance, products, processes or services.

All activities carried out in the context of an integrated project will be defined in the general framework of an ' implementation plan' comprising activities relating to:

- research, and as appropriate technological development and/or demonstration;
- management, dissemination and transfer of knowledge with a view to promoting innovation;
- analysis and assessment of the technologies concerned, as well as the factors relating to their exploitation.

Networks of excellence

The purpose of networks of excellence is to strengthen and develop Community scientific and technological excellence by means of the integration, at European level, of research capacities currently existing or emerging at both national and regional level. Each network will also aim at advancing knowledge in a particular area by assembling a critical mass of expertise. They will foster cooperation between capacities of excellence in universities, research centres, enterprises, including SMEs, and science and technology organisations. The activities concerned will be generally targeted towards long-term, multidisciplinary objectives, rather than predefined results in terms of products, processes or services.

The network proposals should comprise the following elements:

- a general outline of the joint programme of activities, and its content for the first period, broken down into research activities, integration activities, and activities for spreading excellence;
- the role of the participants, identifying the activities and resources that they will integrate;
- the operation of the network (coordination and management of activities);
- the plan for the dissemination of knowledge and the perspectives as regards exploitation of the results.

10. Expressions of interest from the research community

The Commission consulted the research community during 2002 on its readiness to prepare research actions using, in particular, new instruments for topics within the Priority Thematic Areas of Research and in order to identify the most promising and relevant scientific topics for Sixth Framework Programme. This was done by way of an invitation to those research organisations or groups thereof working in the field of life sciences from the Member States, associated countries and other states associated with the EU Framework Programme intending to form consortia (which may also include entities from third countries and international organisations). These were invited to submit an Expression of Interest according to a Guide for Submitters and further details both of this procedure and of the new instruments anticipated for the Sixth Framework Programme may be found at http://www.cordis.lu/fp6/eoi-instruments.

In order to foster the academic and industrial collaboration as outlined above, through technological platforms where multidisciplinary approaches using cutting edge technologies arising from genomic research can lead to more precise diagnosis, individualised treatment and more efficient development pathways for new therapeutic interventions for the 21st century, the Commission invited external experts to analyse the Expressions of Interest received under the heading entitled: 'Application of knowledge and technologies in the field of genomics and biotechnology for health'. However, it should be noted that the Expression of Interest exercise does not imply any kind of pre-selection of proposals or consortia. Projects will be selected on the basis of proposals submitted in response to the call for proposals, on a competitive basis according to the conditions in the formal call for proposals and rules of participation. Account will also be taken of budget limitations, the urgency of the scientific actions, possible overlaps between research topics, final amendments introduced by the Council and the Parliament in the specific programme text and related Commission Services. The topics emerged as being most suitable for these new instruments:

Rational and accelerated development of new, safer and more effective drugs including pharmacogenomics approaches:

- Blood substitutes
- Antiviral therapeutics
- New drugs from novel sources
- Genome based individualised medicines
- Novel therapies for neurodegenerative disorders in CNS and PNS
- Genome-based anti-psychotic therapies
- Signal transduction pathways as targets for disease detection and treatment
- Development of medicines in pediatrics
- Computer-assisted modelling for drug discovery and clinical trials

Development of new diagnostics

- In vivo molecular imaging.
- Reference systems for genetic testing.
- Non-invasive (including prenatal) diagnostics: development of markers for ante- and neonatal screening.

Development of new in vitro tests to replace animal experimentation:

- In vitro alternatives to animal and human toxicology testing
- Development of innovative methods, technology, strategies
- Application of in vitro methods

Development and testing of new preventive and therapeutic tools such as somatic, gene and cell therapies (in particular stem cell therapies) and immunotherapies:

Tissue engineering and regeneration therapies

- Connective tissue disorders: bone diseases, osteoarthritis
- Organ repair: hepatic, haemopoietic, neural tissue
- Biobanks

Stem cells:

- Translation of stem cell biology into new cell-based therapies and novel targets for drug development and other therapeutic products
- Stem cell development for the regeneration of haemopoietic, hepatic, cardiac, neural, mesenchymal and connective tissues
- Stem cell development, technical standardisation, benchmarking, development of reference materials
- Stem cell therapies: standardisation, characterisation and protocol validation.

Immunotherapy: development, testing and response monitoring of immune system-based technologies for application against a wide range of diseases

- New improved vaccine technologies
- Immunotherapy for auto-immune diseases
- Plant based vaccines—plant biotechnology for global health

Gene and cell therapies:

- Viral and non-viral delivery systems
- Cell targeting
- Standardisation and characterisation in gene therapy
- Gene therapy for genetic diseases

Inflammation and immunoregulation:

- Dendritic cells, chemokines, cytokines
- Allergy, autoimmunity, inflammatory disease
- Prevention and treatment of disease through modulation of the immune system

Innovative research in post-genomics, with high potential for application:

Clinical applications of post-genomic information

- Functional analysis of human genome and its application to diagnosis and therapy of diseases, including mitochondrial disorders.
- Adverse reactions to drugs, in particular those of immunological origin.
- Quality and safety control of new tools (gene vectors, stem cells) for clinical use.
- Optimisation, standardisation and quality assessment and assurance of post-genomic technology.

Post-genomic approaches:

- for allergy and autoimmune diseases
- for complex multifactorial diseases
- for the development of new tools for the rapid diagnosis of pathogenic infection and new targets
- for anti-microbial agents
- New strategies for large-scale analysis and high throughput screening in the post-genomic era.
- RNA tools for gene function analysis

Of those topics that emerge under the first of these categories, a number of issues have become clear. New targets of drug discovery programmes, as based on technological platforms in the field of genomics and biotechnology for health, will need to deliver more powerful medicines adapted or tailor-made to an individual's genetic makeup and that can be targeted to specific organs with a significantly decreased like-

lihood of potentially life-threatening adverse reactions. In the preventive field, emerging challenges consist of the development of vaccines composed of genetic material—either DNA or RNA—which would be capable of priming the immune system against potential pathogens without the concomitant risk of developing infection. Similarly, a more precise screening process in susceptible populations for genetically inherited diseases will be necessary in order to enable environmental and lifestyle changes to be introduced at an earlier stage to lessen or eliminate potentially irreversible consequences.

New diagnostic instruments will need not only to develop new tools and non-invasive methods for early diagnosis and monitoring of disease, but also to standardise test results, so as to widen the field of potential applications. These should include in vivo molecular imaging of gene expression, with deliverables such as molecular markers for diagnostics, profiling of new synthetic illicit drugs and drug interaction studies.

In the field of gene transfer, new priorities consist of broadening horizons to include in the treatment of disorders such as non-haemopoietic cancers, cardiovascular, neurodegenerative, infectious diseases and even traumatic tissue alterations. A central issue to be redressed will consist of relating the genetic components of complex disease processes to epidemiological factors, using functional genomics testing in whole populations, with the technological and methodological tools applicable being made available to the scientific community. These would consist of databanks of human tissue samples to be used as reference standards and investigational protocols for future research.

11. Horizontal issues to be assessed

During the implementation of the Sixth Framework Programme and in the research activities arising from it, all fundamental ethical principles will be respected. Due account will also be taken of gender/sex issues as appropriate, child health and childhood diseases as well as innovation and the exploitation of knowledge generated from funded projects.

An integral component of creating the European Research Area shall be to enhance its biotechnology industry in line with the conclusions of the Lisbon, Barcelona and Stockholm European Councils. All activities that can improve framework conditions for innovation in the health sector of the biotechnology industry, especially in SMEs, shall be organised so as to stimulate entrepreneurship and opportunities for investment through venture capital and the involvement of the European Investment Bank. Regulatory bottlenecks in the development of new applications for genomics will be streamlined and ethical implications anticipated as early as possible as well as the broader implications of developments in genomics research for society and citizens.

12. Conclusions

Based on the progress and outcome of the Sixth Framework Programme, the Commission will review the coherence of Community policies and legislation affecting life sciences and biotechnology and launch initiatives and proposals as appropriate. Regulation on life sciences and biotechnology will adequately integrate Community international objectives as well as facilitating innovation and European international competitiveness. In addition, research will be made to contribute coherently and effectively to Community objectives and policies affecting the environment, public health and consumer protection, education, employment, agriculture, trade and development will adequately reflect its long-term and global importance. The Commission will evaluate whether existing international fora and bilateral dialogues are sufficiently effective and provide adequate flow of information, and whether the domestic coordination mechanisms can be improved.

References

[1] A. Aguilar, Drugs of the Future 27 (2002) 26.
[2] Official Journal of the European Communities C64 (2002).
[3] Official Journal of the European Communities L232 (2002) (1–33).
[4] Official Journal of the European Communities C181 (2002) (1–71).
[5] 'Cell Factory': Community Funded Projects (Volume I), Office for Official Publications of the European Communities, 2002.
[6] 'Cell Factory': Community Funded Projects (Volume II), Office for Official Publications of the European Communities, 2002.
[7] Life Sciences and Biotechnology: A Strategy for Europe, Communication from the Commission to the European Parliament, the Council, the Economic and Social Committee and the Committee of the regions, COM(2002) 27.
[8] 'Beyond Borders', The Global Biotechnology Report 2002.
[9] Innovation and Competitiveness in European Biotechnology, Enterprise Papers No. 7, 2002, Enterprise Directorate General, European Commission.