ESFRI

European Strategy Forum
on Research Infrastructures

Roadmap for European Research Infrastructure

Report of the Biology and Medical Science Roadmap Working Group

October 2006

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Foreword

On behalf of the Biology and Medical Science Roadmap Working Group (BMS RWG), I am pleased to present to ESFRI this Report recommending new or upgraded research infrastructure at European level for biology and medical science which we recommend should be included in the first Roadmap for European Research Infrastructure.

The recommendations of the report are based on the work of three expert groups established by the BMS RWG to examine the scientific and business case for new or upgraded research infrastructure in biology and medical science. The expert groups were established by the BMS RWG to examine the research infrastructure needs in Genomics, Bio–informatics, Animal Resources, Structural and Chemical Biology (chaired by Professor Taina Pihlajaniemi), in Clinical and Translational Research (chaired by Professor Liselotte Højgaard), and in Biodiversity and the Environment, (chaired by Jean-Baptiste Bergé and then by Jan Marek).

Members of the expert groups were selected on the basis of their scientific expertise, including in science policy development, and their international reputation. They were nominated by ESFRI delegations in a personal capacity. The membership of the expert groups included some of Europe's and the world's outstanding biologists and medical scientists – a list of the members of each group is included in section 3 of the Report. The BMS RWG would like to thank the experts who gave so generously of their time and expertise to the task of recommending research infrastructure for biology and medical science to be included in the Roadmap. The RWG would also like to thank the chairs of the expert groups and Professor Fotis Kafatos, our scientific advisor, for their skill, commitment and insight in guiding the expert groups in their work.

The Report describes the scientific landscape that is giving rise to a requirement for new infrastructure, the process by which the expert groups reached their conclusions, the proposals recommended by the RWG for research infrastructure in biology and medical science that meet the criteria for inclusion in the first ESFRI Roadmap, and the proposals it considers require further elaboration before they can be recommended for inclusion in later iterations of the Roadmap (the emerging proposals.) The RWG would have welcomed more time in which to develop its proposals and considers that some deadlines in the process were unduly onerous.

An earlier draft of this report was discussed at a meeting of the BMS RWG in Copenhagen on 30 May. The BMS RWG agreed that the draft Report, subject to amendments that have since been incorporated, represented a coherent and strategy-led approach to European policy making on new or upgraded research infrastructures in biology and medical science. It agreed that seven proposals for research infrastructure in biology and medical science meet the scientific and maturity criteria for inclusion on the first draft of the Roadmap.

The BMS RWG recommends to ESFRI that these seven proposals be included in the first European Roadmap for Research Infrastructure. It considers that these recommended research infrastructures for biology and medical science complement those recommended by the PSE and HSS RWG and if agreed by ESFRI, would contribute to a comprehensive response to the infrastructure requirements of science at a European level.

The BMS RWG also recommends that the emerging proposals, outlined in this report, be considered further by experts as possible candidates for future drafts of the Roadmap. It proposes to review the process followed in preparing proposals for the first draft of the Roadmap and to make recommendations to ESFRI as to how the process for the next phase can be enhanced.

Ruth Barrington PhD,

Chair BMS RWG

1. Executive Summary

The Scientific Landscape

Our era has been described as the 'Century of Biology'. The life sciences are undergoing a profound transformation, triggered by the recombinant DNA revolution and amplified by advances in high-throughput analytic techniques such as genomics and proteomics that are rapidly expanding our knowledge of living organisms. The transformation of the life sciences has brought unity to disciplines that were previously distinct. Molecular approaches have illuminated the multiple aspects of the dynamic organisation of living matter across widely different scales, from the molecule to the cell, from the organism to the biosphere. The diversity of life, probably numbering more than ten million species, is counterbalanced by the common descent of all species through evolution. This common descent is reflected in shared lineages of molecules, biochemical pathways, regulatory process and signals. The understanding of this shared heritage vastly accelerates the transfer of knowledge from diverse organisms such as microbes to humans.

The understanding of the common descent of organisms is being powered by major technological advances. In particular, genomics and modern RNA-based 'reverse' genetics have empowered biologists to study in depth not just simple systems such as viruses and microbes but virtually any organism, including humans. This has opened up new avenues of comparative biology which take the understanding of how different systems work and how processes of life and their variations have survived the evolutionary process to understand the living world and to design new cures and effective interventions. These advances have brought biology and medicine into a profound integration. This is the promise and excitement of translational research, whereby the understanding gained from and the tools developed in basic biology become the springboard for novel approaches to understand, preserve and repair the healthy functioning of the human body.

Ever since the development of high-throughput methods for sequencing and synthesis of DNA and proteins, for high resolution imaging and other methods of data capture on a large scale, biology and medical science have become an information science. Modern life sciences are inconceivable without access to well structured, continuously upgraded and freely accessible databases. Bio-informatics is now a prerequisite for all experimental and applied biology, including drug discovery, human genetics and epidemiology. Structural biology is forging a critical path between genetic information and its use or therapeutic interventions.

The expanded scope and depth of the life sciences is also breaking down boundaries with physical, engineering and the mathematical sciences. Novel interdisciplinary approaches include biological and functional imaging, chemical biology, bioengineering and nano-biotechnology. The new field of systems biology is arising as a fusion of biology, modelling and simulation from the computational and mathematical sciences and control theory rooted in physics.

This is the scientific landscape against which the expert groups and the BMS RWG prepared proposals for research infrastructure. The RWG was acutely aware of the current dearth of European-scale infrastructure to meet the rapidly expanding requirements of biology and medical science that will give European researchers an advantage in this globally strategic and competitive field. Most existing infrastructure supports national or institutional needs but is not constructed to deal with European-scale requirements. The infrastructures the RWG recommends for inclusion in the Roadmap meet some of the most urgent needs of life science researchers in Europe. The 'emerging' proposals signal those additional infrastructures that need to be put in place if biology and medical science in Europe is to remain competitive internationally. European scientists have made a major contribution to the transformation of the life sciences as described above. If they are to make a similar contribution in the future, they need the support of infrastructure that compares with the best in the world.

The kind of infrastructure required for biology and medical science differs from research infrastructure as traditionally understood in the physical and engineering sciences. The infrastructure needed for biology and medical sciences tends to be multi-site facilities and to consist of collections of data underpinned by systems for collection, storage and access and that require continuous upgrades over time. The distributed nature of most of the research infrastructures for biology and medical science means that many different countries and institutions can participate in their establishment or in their development. The cost involved in providing infrastructure for biology and medical science is not so much in 'construction' as in maintaining and developing the facilities. Infrastructure for biology and medical science will not need to be 'decommissioned' in the way infrastructure in the physical and engineering sciences need to as technology changes: instead they may need to be 'recommissioned' as they are expanded, take on new functions or are transferred from one responsible operator to another.

Analysis by Expert Groups

The BMS RWG established three expert groups to examine the research infrastructure needs in Genomics, Bio-informatics and related fields (chaired by Professor Taina Pihlajaniemi), in Clinical and Translational Research (chaired by Professor Liselotte Højgaard), and in Biodiversity and the Environment chaired first by Jean-Baptiste Bergé and then by Jan Marek). Members of the Expert Groups were selected on the basis of their expertise, including science policy development, and their international reputation. They were nominated by ESFRI delegations in a personal capacity. The membership of the expert groups included some of Europe's and the world's leading biologists and medical scientists.

The expert groups reviewed, on the basis of existing information, the needs of the potential user scientific community/ies within the next 10 to 20 years and assessed identified research infrastructure according to the strength of the scientific case and the extent to which the proposed research infrastructure is technologically and financially feasible. In addition, expert groups provided information where possible on any consortium that could support the potential for risks- and costs-sharing, the mechanisms for other partners to join later on, and to ensure the use and continuous upgrade of the research infrastructure in the most open and effective way. The expert groups recommended seven mature proposals for inclusion on the first draft of the Roadmap and seven 'emerging' proposals that require more analysis and elaboration.

Proposals for BMS Research Infrastructure

Having considered the recommendations of the expert groups, the BMS RWG recommends seven research infrastructures for biology and medical science that meet the ESFRI criteria for inclusion on the European Roadmap for Research Infrastructure. The RWG emphasises that this list of seven is by no means all the infrastructure required at European level for biology and medical science. The infrastructures proposed have been influenced by the need to demonstrate maturity under the ESFRI criteria, the priorities of member states as demonstrated by the ESFRI call for proposals in 2004, the ESFRI list of opportunities and the resources available to support the work of the expert groups. The proposals presented as 'emerging' later in the report provide a sign-post to the additional research infrastructure that is required for biology and medical science at European level.

The RWG wishes to stress that the process of developing the recommended infrastructures should not be closed and exclusive, but each infrastructure should be open to future partners and participants at a later stage, as well as to new member states.

A number of the proposals recommended have strong potential to produce intellectual property, support technology transfer and to involve and support the European pharmaceutical, medical device, computer and instrumentation industry. For this reason, the BMS RWG considers that investment in the recommended infrastructures will make a major contribution to the competitiveness of Europe's industry and will support the achievement of the Lisbon targets.

European Bio-informatics Infrastructure

The proposed infrastructure will ensure free provision at European level of bio-informatic data to the entire scientific community and related industries. It will encompass an interlinked collection of robust and well-structured and evaluated core databases, capable of accommodating the ongoing massive accumulation and diversification of data pertinent to the biologist.

It will encompass the necessary major computer infrastructure to store and organise this data in a way suitable for rapid search and access, and will provide a sophisticated but user-friendly portal for users. It will be embedded in a database-related research programme that supports the development of critically important standards, ontologies and novel information resources. It will also link to distributed organism-specific knowledge resources and, as appropriate, to speciality and emerging databases of wide interest (e.g. image collections). It will represent a secure but rapidly evolving platform for data collection, storage, annotation, validation, dissemination and utilisation, consistent with the unique requirements of shared resources in the life sciences.

The proposed infrastructure is based around a substantial upgrade to the existing European Bioinformatics Institute (EBI). Primary data resources are now so large and growing so rapidly that handling them in one place is most appropriate. Secondary data resources, that organise and annotate these primary resources to add value to them, are distributed across Europe and make the most of the diverse expertise of its scientists. The proposal seeks to ensure that valuable secondary resources are stably supported and that the entire collection of resources is well integrated.

European Integrated Structural Biology Infrastructure

One of the grand challenges in biology is to combine *integrated structural biology* with cell biology so that an atomic level dissection of the cell can be reconstituted into a functional system. A major aim of this infrastructure is to move structural biology from the study of single protein molecules to the study of the more complex systems used by cells with the long-term aim of using structural biology, together with cell and systems biology, to describe in detail how a cell functions.

This infrastructure will provide a central framework at European level for biology and pharmaceuticals in the twenty-first century. At this early stage much of the work must be at the level of providing an understanding of the structure and dynamics of individual proteins, protein complexes and how they control fundamental cellular processes. This will be achieved, in some cases using model systems, by close linkage with medical and biological research, as far as possible focused on human health, such as cancer, infectious diseases and host-pathogen interactions, and/or environmental problems, such as adaptation of life to extreme conditions of temperature, heavy metals, radiation and toxic molecules.

This grand challenge will be addressed by building a pan-European infrastructure of distributed, integrated Structural Biology Centres, linked in a network. The Centres will combine excellence in structural biology with specific technologic and developmental tasks. The Centres will be chosen on the basis of their complementarities and the strength of existing infrastructure, taking into account originality, the importance of the biological questions being addressed and the relevance to European priorities, such as human health, the environment, therapeutic innovation and biotechnologies. The Centres will be open to the European academic and industrial world and will provide, on a project basis, access to production and experimental facilities. The services will include expertise, key advanced technologies, as well as support for innovation. The network will be organized as a pan-European infrastructure with a central scientific and financial management coordinating the centres' activity.

European Bio-banking and Molecular Resources

This proposal aims to build a coordinated, large-scale European infrastructure of biomedically relevant, quality-assessed sample collections for improved pharmaceutical and biomarker research and development, to enhance therapy and prevention of common and rare diseases, including

cancer. Combining broad access and flexible data integration with securely protected access, using genome-wide approaches and broadband automation technology, it will ultimately provide standardised biospecimens, annotated with clinical, molecular and life style data, and offer a platform to expand further resource development. In this area of unique European strength, valuable and irreplaceable national collections typically suffer from under-utilisation due to fragmentation. Major synergism, gain of statistical power and economy of scale will be achieved by interlinking, standardising and harmonising a large variety of well-qualified, up-to date, existing and *de novo* national resources. Such a clinical biobanking network requires the support of parallel access to common, validated reference material, genomic and population-genetic data and molecular resources that are cost-intensive and laborious to generate. In cooperation, clinicians, pathologists and molecular biologists can thus build a Europe-wide, globally unmatched platform for translational medical research, to speed up development of personalised medication and prevention.

Infrafrontier: Functional Genomics in the Mouse as a Model of Human Disease

The fields of functional genomics, medically related life sciences and systems biology use the mouse as a model system to understand the molecular basis of health and disease in man. In the coming decade, saturation mutagenesis in the mouse will be one of the major tasks of the scientific community and will require a dramatic change in the way of phenotyping and archiving of mouse models. Infrafrontier will organise two complementary and linked European infrastructure networks for large scale and comprehensive phenotyping (Phenomefrontier) and archiving (Archivefrontier) of mouse models. Infrafrontier will be embedded in a global effort to standardise and optimise the phenotypic characterisation of medically relevant models and also state of the art archiving and dissemination of such. Thus, Infrafrontier will provide the umbrella of a pan-European effort to standardise and optimise the phenotypic characterisation of medically relevant mouse models and a state of the art archiving and dissemination of such important biological samples.

EATRIS - European Advanced Translational Research Infrastructure for Medicine

This infrastructure addresses the challenge at European level of 'translating' advances in biology into new therapies and diagnostics that are of benefit to human health. It proposes the establishment of a consortium built on an initial core of advanced research centers in Europe that have already established a strong reputation in applying scientific advances to diseases that are of major importance to the European population, such as cancer, cardiovascular disease and metabolic disorders. The consortium, which will gradually be expanded, will have as its primary goal the promotion of the transfer of research findings into clinical practice. It will help secure for the European Union an international leading position in the most important field of translational medical research. It will also considerably strengthen the economic potential of health care markets in Europe, with a strong emphasis on "technology transfer" from research to industry.

Network of Distributed Infrastructures for Clinical Trials and GMP biotherapy facilities in Europe

This infrastructure will provide for the interconnection at European level of national networks of clinical research centres and clinical trial units, through a multinational coordination team, and through European correspondents embedded in the national network of each member state. Shared procedures will enable industry or academic clinical research projects to be carried-out in any medical field, with high-quality Good Clinical Practice standards across the whole EU, thus enlarging and accelerating patient recruitment. It will provide for the upgrade or creation of new facilities supporting the production and the evaluation of innovative biotherapy agents, support professional data centres for high-quality data management across the EU and facilitate connections with disease-oriented patient associations and registries, as well as disease-oriented investigator networks, in order to foster patients' enrolment.

Life Watch - An Infrastructure for Monitoring European Biodiversity

This infrastructure, which will be open-access, will put in place the essential infrastructure and information systems at European level necessary to collate both existing and new data on biodiversity and distribute this information with analytical and modelling capabilities to the scientific community and to other users in the public, commerce and policy sectors. The challenge is to bring together the partly existing, separate components (species-level and ecosystem-level data from observations and from collections; data integration facilities; on-line analytical and modelling tools) and to add scientific value for the next generation infrastructure, operating as an observatory of our environment. It is not a matter of just merging the components, but to organise and manage these in a setting that allows for advanced data mining and knowledge development.

The components are categorised as follows:

- Infrastructure networks for data generation and data processing
- Facilities for data integration and interoperability (and scientific domain interaction)
- Virtual laboratories to allow for utilising a range of analytical and modelling tools
- Service Centre to provide special services for European and national policies, and to provide research opportunities for young scientists.

BMS Emerging Proposals

The BMS RWG has identified seven proposals as promising infrastructure for biology and medical science at European level but which at present lack the necessary maturity to be recommended as mature proposals on the first draft of the Roadmap. However, they should be listed on the Roadmap as 'emerging' proposals requiring further analysis and development. The BMS RWG considers that these proposals should be examined by expert groups in the context of preparing the next draft of the Roadmap. The proposals identified as emerging are:

European Infrastructure for Chemical Biology

This infrastructure will incorporate a European Molecular Library Resource Centre (EMLRC) and a European resource for Ligand Binders against the Human Proteome. The EMLRC will involve the Europe-wide coordinated acquisition and collection, maintenance, dissemination, application, validation and information storage of small molecule tools to advance basic research in life sciences. It will contract with chemists to provide unique and special compounds to be included into a central repository for biological activity profiling. It will enhance and promote access to Europe's compound repository and screening technologies for all biologists submitting their biological assays. Data of supported research projects will be collected in a central database of biological activities of chemical compounds made available to the public. This database will be an extremely valuable treasure for future drug development in Europe.

European Infrastructure for Systems Biology

After two decades of genomic research, many of the molecular components of human cells, including those implicated in disease, have been deciphered or will become available in the foreseeable future. Despite this wealth of data, a systems level understanding is still largely missing. The general focus of biomedical research needs to change from primarily a component-by-component analysis at the molecular level to a systems biology level, capturing the characteristic network dynamics behavior, and thus providing a much more comprehensive understanding. This has specific implications for complex diseases, for which the underlying genetic basis is related to combinatorial interactions of multiple genes. This paradigm shift in biomedical research cannot be achieved by a few isolated research teams but requires the establishment of a European infrastructure for systems biology.

Advanced Light Microscopy for Europe

The purpose of this infrastructure is to generate and apply novel advanced technology for non-invasive imaging of biomolecular function in living systems ranging from single cells to model animals by establishing advanced light microscopy imaging centers in Europe. With the explosion in the use of digital imaging techniques in basic research, the funding necessary to establish the required infrastructure and human expertise exceeds considerably both the financial and scientific capabilities of individual laboratories or even of institutions. To address the problem of resource fragmentation, the proposed infrastructure will organise distributed but interlinked Integrated Biological Imaging Centers of excellence in nearly every member state, so that all basic science research laboratories would have access to the latest technology and expertise.

European Infrastructure for Synthetic Biology

A new infrastructure to support synthetic biology in Europe is essential to develop momentum and consolidate progress in this research field which has enormous strategic importance for Europe. The objective would be to provide key service functions to the synthetic biology community, to enable standardisation of biological parts on which synthetic biologists can draw, including the provision of reference methods and materials, as well as associated research and top level training.

EIRBI: European Infrastructure for Research in Biomedical Imaging

The field of biomedical imaging is challenged to translate the tremendous achievements of molecular biology into early diagnosis and efficient follow-up of therapeutic treatments as well as developing novel imaging-guided drug delivery and minimally invasive treatments. The establishment of a European Infrastructure for Research in Biomedical Imaging is essential to maintain the competitiveness of European academic institutions and industries and should allow a leading role for Europe in the decades to come in a fundamental, rapidly expanding area of science and medicine that will increasingly benefit European citizens, research and industry.

High Security Laboratories for Emerging and Zoonotic Diseases and Threats to Public Health

Recent crises have shown that infectious diseases are far from being eradicated in humans as well as animals. One of the key issues to address in order to protect human health is the boundary between human and animal pathogens. The scientific challenges are enormous but the biotechnological revolution allows for important breakthroughs to be made. Diagnosis, surveillance and research of such diseases and their agents require high-security laboratories (containment level L3 and L4).

ANAEE: European Infrastructure for the Analysis and Experimentation on Ecosystems

This purpose of this infrastructure is to provide the basis for the development of ecosystem science into modern systems biology using *in silico*, *in vitro* and *in natura* experiments to generate and test hypotheses and to make predictions about the environment.

2. Scientific Landscape of Biology and Medical Science and their Infrastructural Requirements

2.1 A Rapidly Changing Landscape

The Life Sciences have undergone a profound transformation in recent years, which is still ongoing. It was triggered by the recombinant DNA revolution and amplified more recently by genomics, proteomics and other high-throughput analytic approaches. This transformation encompasses:

- Unification of previously distinct biological disciplines: Molecular approaches have illuminated the multiple aspects of the dynamic organisation of living matter across widely disparate scales: from the molecule through molecular assemblies and machines, the subcellular organelles, the developing organism and its ceaseless restructuring as it functions, malfunctions and ages. This unification now encompasses pluri-organismic entities and interactions (symbiosis, parasitism, infection and immunity etc); it is spreading into the study of populations of organisms, ecological systems, and the biosphere.

- Unification of understanding across the tree of life: The diversity of life, probably numbering more than 10 million distinct species, is counterbalanced by their common descent through evolution, which is reflected in the persistence of shared lineages of molecules, biochemical pathways, regulatory processes and signals. This shared heritage vastly accelerates the transfer of knowledge concerning highly diverse organisms, from microbes to humans.

- Transition in the focus, from traditional models to all organisms: Whilst this transition is facilitated by the common descent of organisms, it is also powered by major technological advancements. In particular, genomics and modern RNA-based "reverse" genetics have empowered biologists to study in depth not just simple systems (e.g. viruses and microbes) or model systems that have been studied for many years intensely, but virtually any organism, all the way to humans. This has opened up new avenues of comparative biology whereby the more we come to know about how different organisms work, the more we understand the essential processes of life and their variations that have survived evolutionary selection. Such knowledge is valuable for understanding the panorama of the living world, but also for designing cures and improvements, as in the new frontiers of regenerative and synthetic biology.

- Unification of Biology and Medicine: The same transition is bringing medicine into a profound integration with basic biology. This is the promise and excitement of translational research, whereby the understanding gained from and the tools developed in basic biology become the springboard for novel approaches to understand, preserve and repair the healthy functioning of the human body. Indeed, the human species itself is becoming a tractable model system for study, further shortening the distance between laboratory and bedside.

- Emergence of Biology as an information science: Ever since the development of convenient and high-throughput methods for sequencing and synthesis of DNA and proteins, for protein structure analysis, for high-resolution imaging (including functional imaging) and for other methods of data capture on a large scale (the "-omics" revolution), Biology (including Medicine) has become an information science. The modern Life Sciences are inconceivable without recourse to well-structured, continuously upgraded, massively enriched at an exponential rate, and freely accessible databases. Indeed, bioinformatics is now a prerequisite for all experimental and applied biology, including drug discovery, human genetics and epidemiology. Similarly, structural biology is now forging a critical path between genetic information and its utilisation for beneficent interventions.

- Interaction between BMS, Physical, Engineering, Computational and Mathematical Sciences: The same process of restructuring and vastly expanding the scope and depth of the life sciences has begun to breach the boundaries between BMS and the sister sciences. Amongst

the long list of novel interdisciplinary approaches and tools are now well-known examples such as biological and functional imaging at various scales; Chemical biology; Bioengineering, and the coming advances in Nanobiotechnology. The new field of Systems Biology is arising as a fusion of quantitative experimental and "-omics" biology, modelling and simulation grounded in the computational and mathematical sciences, and control theory rooted in physics.

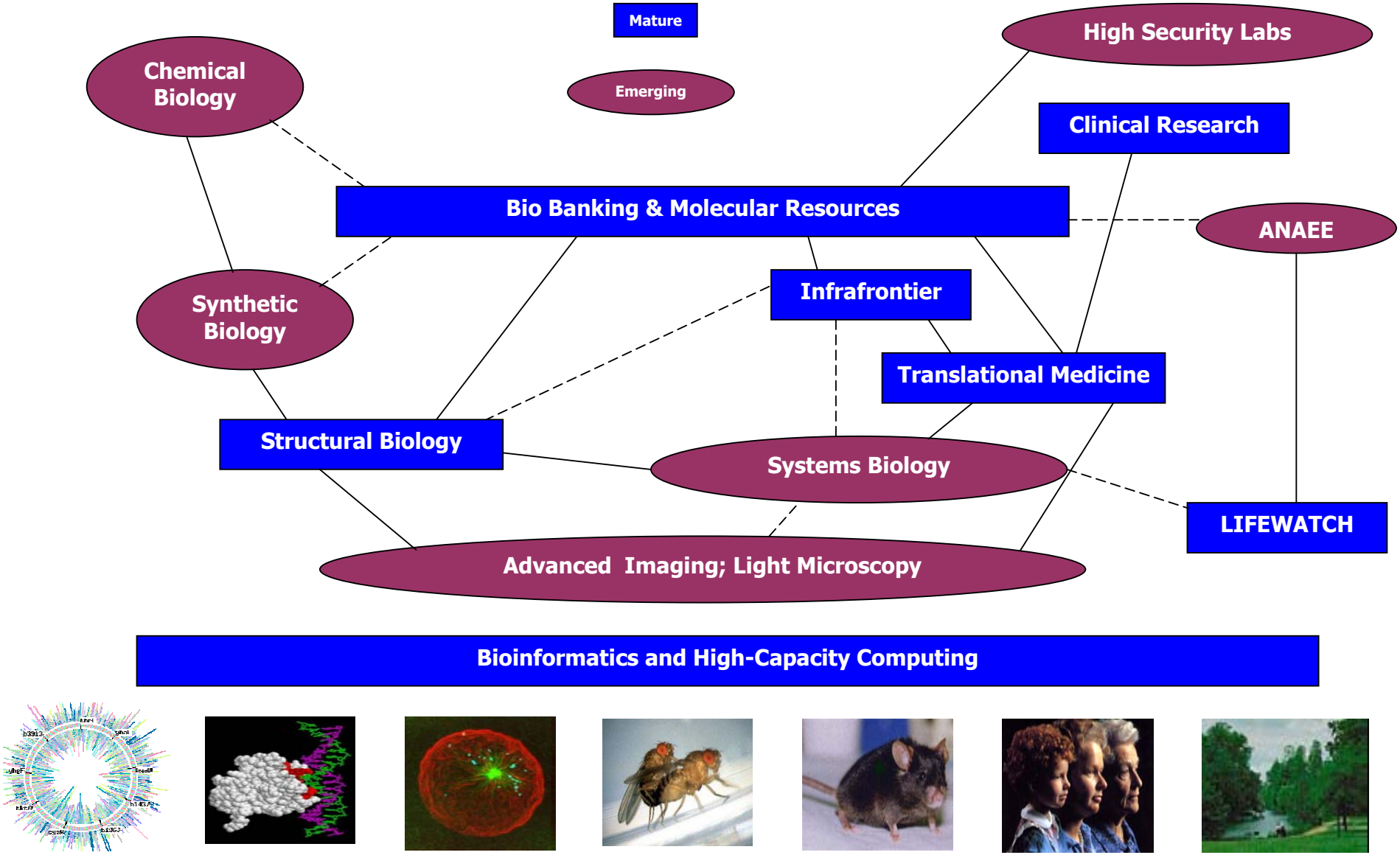
2.2 An Overview of Infrastructural Requirements

The massive restructuring and expansion of the BMS in what has been called "the century of Biology" are accompanied by major infrastructural requirements. A token of this realisation is the degree to which new or upgraded infrastructures for the Life Sciences are coming to dominate the infrastructural investment plans in other continents e.g. in Australia's government plans for research infrastructure, where the major focus is on the life sciences. Importantly, the BMS infrastructures are largely different in nature from those of the physical sciences. Instead of a massive physical project/collection of new instruments, they involve data collection, storage and access systems which not only require long-term maintenance and operation, but also continuous upgrades. Thus, even if they require upfront investments that are usually significantly smaller than those for physical sciences infrastructures, over time they require comparable or even larger investments. Furthermore, they are often (but not invariably) multi-site infrastructures. For example, whilst synchrotrons and the new generations of colliders have massive upfront design and construction costs, most of the BMS infrastructures (e.g. for bioinformatics) require successive investments for major upgrades over a considerable time. Indeed, unlike physical sciences infrastructures which frequently have a foreseen limited lifetime and require provision of funds for decommissioning, the bioinformatics infrastructure is one that will continue to expand (albeit with a reduction of unit costs), and will remain the depository of biological information for as long as we now can foresee. Such infrastructures require no decommissioning costs. However, if the operator proves less than satisfactory there will be "recommissioning" costs for transferring the infrastructure to a new operator (this has already happened with the structural biology infrastructure "Protein Data Bank" in the United States.)

Biodiversity is essential for sustaining human life and well-being. It is crucial to sustaining livelihood and has a vital role to play as a provider of natural capital, goods and services. However, biodiversity is also being lost at an alarming rate in the EU and globally effective action is needed to meet the EU's 2010 policy target to halt biodiversity loss. Biodiversity research infrastructures are required to support cross-sectoral policies that depend on the sustainable use of biodiversity, support the ecosystem approach to the management of fisheries, aquaculture, forests and agricultural systems, and to develop and assess methods to achieve sustainable lifestyles that reduce the impact on biodiversity. They must include the development of inter-operable systems to provide access to, and analysis and dissemination of, a wide range of data from distributed sources and, furthermore, large-scale *in vitro* controlled environment facilities enabling experimental and controlled manipulation ecosystems. The access to long-term data from distributed observation systems and biological collections is needed to provide information on the status of biodiversity across Europe, as well as an improved understanding of the major anthropogenic and natural drivers and pressures affecting biodiversity as a basis for predicting future changes, and to help resolve cross-sectoral policy dilemmas.

There are currently no European scale research infrastructures addressing these needs. Existing infrastructures currently support national or institutional needs but are not constructed to deal with European-scale requirements. For instance, demands for biological information are growing rapidly and the existing structures to collect, deliver and analyse these data are fragmented. The biodiversity research community relies on data and information from distributed sources and one of the main challenges is to develop the infrastructures required to ensure that these data are collected in harmonised ways and made accessible to the research communities. In other cases centralised infrastructure may be required to bring together a critical mass of researchers and facilities. For example: to provide large-scale facilities for controlled experiments on the relationship between biodiversity and ecosystem functions; the development of new technologies for biodiversity assessment; and for knowledge management and technology transfer on sustainable biodiversity use.

Diagrammatic representation of Research Infrastructures within the BMS Landscape



3. Analysis of the Expert Groups

3.1 Expert Group on Genomics, Bio-Informatics and related fields (EGGB)

The EGGB worked from November 2005 to April 2006 including a single one-day meeting, two two-day meetings and a joint session with the Expert Group on Clinical and Translational Research. In its work, the Expert Group followed the set "Terms of reference of expert groups and chairpersons". The expert group has reviewed the needs of the biological and medical scientific communities for pan-European infrastructures and it has analysed specific initiatives received through ESFRI.

The mandate of the EGGB was to review and suggest proposals for new research infrastructures and major upgrades of pre-existing research infrastructures. In this respect it was seen to act as a bottom-up committee and produce material for the BMS RWG and for the ESFRI Forum. The report of the expert group was initially scheduled for completion by June 2006 and to consist of opinions, suggestions and proposals on topics for future infrastructures. Subsequently, the report deadline was moved forward to 26 April 2006.

3.1.1 Membership of Expert Group

Dr Tim Hubbard, Head of Human Genome Analysis, Wellcome Trust Sanger Institute, UK

Professor Doron Lancet, Director of National Center for Genomics, Israel

Professor Dino Moras, Head of the Structural Biology Laboratory at the IGBMC (Illkirch), France

Professor Mary Osborn, Max Planck Institute for Biophysical Chemistry, Göttingen

Professor John Sulston, Vice-Chair of the UK Human Genetics Commission and Nobel Prize winner in Physiology/Medicine

Professor Dimitrios Thanos, Director of the Institute of Molecular Biology, Genetics and Biotechnology, Foundation for Biomedical Research of the Academy of Athens, Greece

Professor Glauco Tocchini-Valentini, Director of the Italian National Research Council's Institute of Cell Biology (CNR-IBC), Rome

Professor Gertjan Van Ommen, Head of the Department of Human Genetics of Leiden University Medical Center (LUMC) and founder of the Leiden Genome Technology Center, The Netherlands

Professor Taina Pihlajaniemi (Chair), Professor and Chairman of Medical Biochemistry and Molecular Biology and Scientific Director of Biocenter and member of the BMS RWG

3.1.2 Methodology used by Expert Group

The analysis of infrastructures was performed according to the criteria listed by ESFRI. According to the scientific/strategic criteria the infrastructure projects should:

- correspond to a real need for the development of the field in Europe,
- be supported by the appropriate scientific community at European level,
- be of pan-European interest,

- entail multi-user facilities offering an open access (physical or virtual) for scientists from all over Europe, and
- be relevant at international level.

According to the technical and financial criteria the infrastructure projects should:
- be timely and mature,
- be technologically feasible,
- open new possibilities or offer improved technological performance,
- have evaluated construction and operating costs, and
- offer good possibilities for European partnership and commitment of major stakeholders.

The group had general discussions on the nature of the infrastructures and how they could best serve the scientific community. It was concluded that the projects should be target-oriented, the equipments should be part of large target-oriented infrastructures, and there should be competition between different centres. The question was raised about how an infrastructure would finish, an issue which was subsequently deemed inappropriate and not required for BMS infrastructures.

3.1.2.1 The proposals evaluated by the Expert Group

The following proposals were evaluated by the EGGB:

- Over 20 proposals originally submitted to the BMS RWG in 2005 in the areas of genomics, functional genomics, bioinformatics, systems biology, animal resources, proteomics, structural biology and chemical biology.

- The ESFRI List of Opportunities on Biological and Medical Sciences; this list included eight potential research infrastructures. One of the original suggestions of the BMS RWG was omitted by the ESFRI forum, and this proposal in the area of structural biology was included in the analysis. The accepted List of Opportunities is the following:

1. European infrastructure for research in and, protection of, biodiversity,
2. Advanced infrastructure for brain and whole body imaging,
3. Bio-informatics infrastructure for Europe,
4. European network of advanced clinical research centres,
5. European network of bio-banks and genomic resources,
6. High security laboratories for emerging diseases and threats to public health,
7. Infrastructure for functional analysis of a whole mammalian genome, and
8. Model testing facilities for biomedical research

- Additional proposals were provided by ESFRI during the period of the Expert Group and these were included in the analysis.

3.1.2.2 Other material used:

The material used for assessing the needs of the field included:

- The Survey of European Research Infrastructures (http://www.cordis.lu/infrastructures/survey.htm

- Material for the Third European Conference on Research Infrastructures, Nottingham, UK, 6-7th December 2005 (http://www.nottingham.ac.uk/ecriuk/)

- Future Needs for Research Infrastructures in Biomedical Sciences; a report based on a Workshop held in Brussels, 16 March 2005; European Commission, Research Directorate General, Directorate B.

- Towards new research infrastructures for Europe: the ESFRI "List of opportunities"; a March 2005 report by ESFRI. The "List of Opportunities" is a "balanced set of examples of concrete and mature projects for new Research Infrastructures of pan-European interest which could be developed during the course of FP7 (2007-2013).

- Projects funded under the FP6 – Research infrastructure action

- The NIH Roadmap in medicine and biological sciences

- The Australian "National collaborative research infrastructure strategy" (2005)

- Biological Application of Synchrotron Radiation: An Evaluation of the State of the Field in 2002, Issued by the Structural Synchrotron users Organisation, October, 2002

- Relevant articles in scientific journals

3.1.2.3 First step/analysis

As the initial step the EGGB analysed the original proposals and found many of them to overlap in topic. In assessing these it was agreed that a balanced group of infrastructure proposals were included in the ESFRI "List of Opportunities" with the exception of an unjustified omission of an infrastructure for structural biology. Among the topics of the "List of Opportunities" (see above) the Expert Group identified numbers three, seven and eight as belonging to its mandate, numbers four and six were seen to belong to the Expert Group on Clinical and Translational Research, while numbers two and five were shared by these two Expert Groups, and number one was deemed to fall under the area of the Expert Group for Biodiversity and Environment.

The EGGB considered the following topics of highest priority in terms of pan-European infrastructures: bio-informatics, functional analysis of a whole mammalian genome, model testing facilities, structural biology, bio-banks and genomic resources. These topics were selected for more detailed analysis.

Four subgroups were set up, each consisting of two or three members of the Expert Group, to prepare proposals on the basis of the original ESFRI proposals and discussions with the scientific community. In addition to the particular topics listed above, it was emphasised that all proposals and all fields should be covered including chemical biology and systems biology, when the Expert Group would prepare its proposals for the BMS RWG.

The tasks of the subgroups were:
- to evaluate the material submitted to ESFRI, i.e. all proposals submitted,
- to take use of other existing material regarding their tasks as well as consult members of the scientific community,
- to prepare a two page draft of the document "Template for the Expert Groups to detail potential new pan-European research infrastructures to be recommended for ESFRI consideration, and
- to present their evaluation and suggestion to the Expert Group in the next meeting.

3.1.2.4 Second step/analysis

The subgroups reported to the EGGB on their analysis of the proposals on the four previously selected areas, structural biology, bioinformatics, animal models and functional analysis facilities for mouse studies, and biobanks and genomic resources. The topics were evaluated and considered to fulfill the ESFRI criteria for mature proposals. These four proposals were agreed to be further processed using the document "Template for the Expert Groups to detail potential new pan-European research infrastructures to be recommended for ESFRI consideration".

A proposal on rat functional genomics was evaluated as representing a model with high value for physiological and pharmacological studies but not being as yet well developed in terms of gene targeting. This proposal and one concerning a primate infrastructure were not considered to be as high priority as the mouse model at this stage of the ESFRI process.

A general discussion was held on the nature of systems biology and its position among research fields and infrastructures. A general discussion was also held on the nature of chemical biology and existing screening libraries in Europe and America. It was decided that both topics should be processed further.

Moreover, it was decided that the topic of imaging infrastructures should be discussed with the Expert Group on Clinical and Translational Research.

3.1.2.5 Third step/analysis

A joint meeting of the EGGB and the Expert Group on Clinical and Translational Research was held in order to jointly analyse the infrastructure needs of biological and medical areas. Prior to this meeting, draft proposals on bioinformatics, structural biology, animal and functional analysis facilities, biobanks and genomic resources, clinical and translational research centers and systems biology centers were circulated to both groups.

Further processing of the proposals was planned in the joint meeting. The topics of bioinformatics, structural biology and animals were strongly endorsed as mature proposals by the Clinical group. In the joint discussions of both Expert Groups the importance of Bioinformatics for all activities being considered was emphasised, as was the current inadequate support for it in Europe. Both Expert Groups therefore agreed that supporting the Bioinformatics Infrastructure proposal should have the highest priority.

The bio-banks and genomic resources proposal was planned to be jointly prepared by the two Expert Groups as a mature proposal. Imaging relating to basic research was agreed to be processed further by the EGGB.

The EGGB strongly supported the proposals of Translational and Clinical Research Centers developed by the Expert Group for Clinical and Translational Research.

3.1.2.6 Fourth step/analysis

Final modifications of the proposals on bio-informatics, structural biology, animal and functional analysis facilities, bio-banks and genomic resources were agreed. Based on analysis of the science case and the concept case, these four topics were considered as mature infrastructure proposals and should therefore fully qualify for the ESFRI Roadmap.

The EGGB also decided to put forward four emerging proposals, the topics being chemical biology, systems biology, imaging, and synthetic biology.

3.1.2.7 Important Considerations

The life sciences have undergone a profound transformation in recent years, and further rapid developments will characterise the field in the coming years. The Roadmap should reflect "the Century of Biology".

The concept of large-scale infrastructures has largely been applied to physical and engineering sciences. Thus, there has been an historical emphasis of infrastructure funding on the physical and engineering sciences while other disciplines have received only very small portions of such funding. This strong emphasis on infrastructure funding on physical sciences is typical in Europe, whereas in USA the biological and medical sciences are proportionally much more strongly represented in such funding. Moreover, the recent plans for infrastructure policies in Australia lay a strong emphasis on biological and medical sciences.

The research infrastructures in biological and medical sciences are typically of a distributed nature, and the up-front investments are smaller than in physical sciences. However, there is a necessity of continuous up-grades and funding encompassing the rapid developments in the field. The EGGB strongly emphasises the need of taking into account the special nature of infrastructures for biological and medical sciences when preparing the Roadmap. Given the rapid development of these research fields, in particular the potential impact of medical research outputs on public health, the EGGB felt there was a strong argument for the proportion of EU funding devoted to biological and medical infrastructures to be substantially increased towards parity with the physical sciences.

The EGGB was greatly concerned that the requirements regarding funding commitments for the projects in the first draft of the Roadmap were more appropriate for research infrastructures in the physical and engineering sciences than for other fields. An important point is that the time allowed for securing the key stakeholders was too short and therefore appropriate measures should have been adopted in order to secure the inclusion of the mature proposals in biological and medical sciences.

A strong argument was raised that the proportion of EU funding for preparatory and construction costs of infrastructures in biological and medical sciences should be over 20 per cent of the total budget because of the rapid development of these research fields.

It was also emphasised that in biological and medical sciences the costs should be clearly divided to construction and continuous upgrading of an infrastructure, the latter being fundamental for ensuring that the biological and medical infrastructures are up-to-date.

A serious concern was expressed concerning the short-term support for infrastructures for biological and medical sciences which may be deleterious for collections and databases. A new phrase 'recommissioning' was suggested for a program where infrastructures can be shifted or reopened in another institution in the event of the original institution forfeiting responsibility. This would also encompass further development and up-grades of existing infrastructures.

It was pointed out that the infrastructures are usually beneficial to big research centres and new mechanisms should be created to support smaller research institutions and individual scientists. A small portion of the expected infrastructure funding should be reserved for bottom-up applications for small-scale equipments and research initiatives. This funding should be independent of national and intergovernmental agencies.

3.1.3 Conclusions/Overview of the Research Infrastructure Proposals

The EGGB proposed **four mature projects** to be included in the infrastructure Roadmap at its first stage. These four projects should be started immediately in order to ensure a competitive position for European research in biological and medical sciences. All proposed infrastructures are distributed facilities with operations in several European countries. The first three proposals are major up-grades of existing facilities, but these also include establishment of new nodes of operation. The fourth proposal represents a new pan-European infrastructure.

The EGGB stressed that key players involved in each of the proposals should be speedily identified by the BMS RWG and they should be allocated the task of preparing any necessary further details regarding the proposals.

The four mature proposals are:

- Bioinformatics infrastructure for Europe

Bioinformatics are at the heart of modern life sciences. There are several scales of databases: class 1 databases are fundamental archives, such as DNA sequence archives, class 2 databases are wide, but not as functional as the class 1 databases. Class 3 databases have a restricted amount of data and they are not in wide use. Class 1 centres have computers and system facilities to create new databases without need of copying data. These class 1 databases form the suggested infrastructure.

The proposal "Bio-informatics Infrastructure for Europe" is a major upgrade of an existing infrastructure, the European Bioinformatics Institute (EBI). EBI serves the global science community by providing essential databases, in particular DNA sequence archives. The proposal combines existing databases and needs on-going support for its maintenance, but also incorporating new aspects.

- Infrafrontier: functional genomics in the mouse as a model of human disease

The mouse is the central model organism used for understanding physiology and pathobiology of diseases affecting man and for development of new therapies. The proposed model builds on the pre-existing European infrastructure EMMA, and the Phenomefrontier and Archivefrontier programs, and it will form a complementary and interlinked network of centres. The multiple centre model is crucial for the safety and security of the archives. The importance of collaboration over the three continents, Europe, America and Asia is emphasised. On the other hand, the importance of building and maintaining national mouse clinics and even research topic-based phenotyping laboratories were recognised as necessary institutions where special research problems can be analysed and phenotyping deepened.

- Integrated structural biology infrastructure for Europe

The first step in the development of structural biology was descriptive. Now structural biology is changing towards a problem-based approach where sample preparation, biological characterisation and functional analysis are integrated with the structural studies. The proposal does not suggest a single big instrument centre, but rather a few overlapping, complementary centres to form the infrastructure. The centres should be near strong biological research institutes where expertise is available to support the infrastructure. NMR, X-ray crystallography and cryoelectron microscopy were seen as important tools for structural biologists, whereas synchrotrons can be shared with physicists.

- European network of biobanks and genomic resources

Biobanks are widely considered as a key resource in unravelling the association between disease subtypes and small, but systematic variation in genotype, phenotype and lifestyle. The proposal stresses the importance of combining tissue specimens, genetic information and life style information leading to the generation of a globally unmatched platform for translational research. The proposal also emphasises vertical integration of resources from different organisms and tools for every single gene.

The EGGB proposes **four emerging projects** to be included in the infrastructure roadmap at later stages. These proposals represent important areas but at present the plans are not mature. The EGGB suggests that the emerging proposals should be followed up by further preparation and their inclusion in the Roadmap at a later stage is recommended.

3.2 Expert Group on Clinical and Translational Research (EGCT)

The EGCT worked under the responsibility of the BMS RWG. It was focused on clinical and translational research including imaging, with the items on the BMS RWG "List of opportunities" as the focus area. During seven months the EGCT met three times and two mature proposals and one emerging proposal materialized. One joint meeting was held with the EGGB.

The EGCT applied the selection criteria of scientific excellence and relevance for the biomedical area in Europe. These include aspects such as international competitiveness, economic potential and European markets.

The selection process was based on three steps:

- preliminary discussion
- interactive finalising of proposal
- final discussion with major stakeholders

3.2.1 Membership of Expert Group

Professor Anita Aperia, Professor of Pediatrics at Karolinska Institutet. Astrid Lindgren Children's Hospital, Stockholm, Sweden

Professor Dimitrios Boumpas, Chairman of the European League against Rheumatism (EULAR)

Professor Silvio Aime, Professor of General and Inorganic Chemistry and Head of the Center of Molecular Imaging at the University of Torino, Italy

Professor Herbert M. Pinedo, Director of the VUmc Cancer Center Amsterdam, The Netherlands

Professor Eero Vuorio, Chancellor of the University of Turku, Finland

Professor Christian Ohmann, Head of the Coordination Centre for Clinical Trials at the Heinrich-Heine-University Düsseldorf, Germany

Professor Otmar D. Wiestler, Chairman and Scientific Member of the Management Board of Deutsches Krebsforschungszentrum (German Cancer Research Center, DKFZ), Heidelberg

Professor Liselotte Højgaard (Chair) Director and Professor, Clinical Physiology, Nuclear medicine & PET Rigshospitalet, University of Copenhagen and member of the BMS RWG

3.2.2 Methodology used by Expert Group

The methodology used by EGCT for selection of proposals submitted to the expert Groups was based on the ESFRI roadmap criteria, an evaluation of the proposals behind the "List of opportunities" and discussion among EGCT members. Selection was done in three steps:

First step: preliminary evaluation of proposals submitted in the "List of opportunities"

Second step: merging of proposals from the "List of opportunities", chosen on the basis of scientific excellence and the need for a European research area in clinical and translational medicine

Third step: finalising of merged proposals. The proposal on biobanking was edited in collaboration with the EGGB. The proposals were finalised in accordance with the ESFRI document: "Summary of the rules for making the Roadmap".

3.2.2.1 First step/analysis

The following is the list of proposals that were evaluated in the first step:

- European Institute on Drug Abuse (EIDA)

- Clinical Research Centres (CRCs)

- High security laboratories for infectious diseases

- European Centre for Training & Research on Imported and Highly Contagious Diseases (EUTRICOD)

- European Brain and Behaviour Centre (EBBC)

- Advanced Light Microscopy Applications (ALMA)

- European initiative of biobanking

- EC – transIT: European Center for Transplantation and Immunotyping

- European Biomedical Imaging Center (EBIC)

- Infrastructure for Brain mapping in Europe, very high field NMR (NeuroSpin)

- A Multidisciplinary and international centre of excellence in molecular imaging

- European Centre for Multimodal Molecular Neuroimaging and Therapy (EC-MMNIT)

- European Infrastructure for Research in Biomedical Imaging (EIRBI)

- Longevity and Aging Centre (LAC)

- European Centres of Clinical Research and Translation

- BioInfoMed Research infrastructure (BIM)

- European Cancer Survival Databanks

- MedAustron

- European Biopharmaceutical BMP Process Centre (EBGPC)

Criteria

The EGCT used the ESFRI document "Criteria for entering the Roadmap process" for the first step selection. The criteria stipulated that the proposed infrastructure must be:

- A Major infrastructure for the particular scientific community
- A Multi-user facility

- Of Pan-European interest
- Backed by a Research Programme agreed by the appropriate community
- Technological feasibility
- Multi-annual funding
- Mature based on appropriate science case, technical case and business case

The evaluated proposals were placed into two categories:

Considered "interesting", which could enter the Roadmap:

- Infrastructure for clinical research and clinical trials
- Infrastructure for translational research
- Infrastructure for biobanking
- Infrastructure for imaging

Considered beyond the expertise of the Expert Group for Environment and Biodiversity

- High-security laboratories

It should be noted that the proposal for EATRIS "The European Advanced Translational Research Infrastructure" was initially pursued in combination with the network of clinical trial centres proposal. However, as this proposal taken together was deemed so big as to render it almost impossible to organise, it was decided to introduce two major individual proposals instead; one for clinical trials: "Network of Distributed Infrastructures for Clinical Trials in Europe" and one for translational research: "EATRIS - The European Advanced Translational Research Infrastructure". The bio-banking proposal was prepared in collaboration with the EGGB (see section 3.1).

3.2.2.2 Second step/analysis

For the finalising of the proposal on biobanking and for comments on the other two proposals, a joint meeting was held in Brussels on the ninth of March 2006 with participants both from the EGCT and the EGGB. The biobanks proposal was strongly supported by both groups and finalised with members from both expert groups. The proposal on translational research (EATRIS) was strongly supported by the EGGB and it was stressed that the communication and sharing of knowledge between basic and fundamental science in biology, medicine and clinical research in hospitals is very poor, especially in Europe.

3.2.2.3 Third step/analysis

The proposals were finalised in an iterative process with all members of the EGCT and in consultations with Professor Fotis Kafatos and Dr Ruth Barrington, BMS scientific advisor and Chair respectively.

3.2.3 Conclusions/Overview of Proposed Infrastructures

Based on the methodology mentioned above, the EGCT concluded that:

1. The proposal EATRIS "The European advanced translational research infrastructure in medicine" is mature and is strongly recommended by the EGCT to be included in the Roadmap.

2. The proposal "European biobanking and molecular resources infrastructure" is mature and strongly recommended by the EGCT to be included in the Roadmap.

3. The proposal "Network of distributed infrastructures for clinical trials in Europe" is mature for inclusion in the Roadmap.

4. The proposal "EIRBI – European infrastructure for research in biomedical imaging" is recommended as a strong emerging proposal and should be further considered for inclusion in subsequent editions of the Roadmap.

Rationale

The pharmaceutical industry in Europe was formerly the world leader, but at present there are few new products in the European pipeline, and in recent years the European Pharmaceutical Industry has launched only a few important new drugs. European clinical research has been challenged by an increasing demand for efficiency in hospitals and new governmental rules and regulations, making it difficult to conduct trials. Heavy competition from the life science area in the US threatens to further set back the clinical and translational research area in Europe. A significant deficit can particularly be observed in translational biomedical research, (where results are transferred from basic science into patient care), compared to the US, where translational research centers with approximately 70 dedicated translational research infrastructures have been set up. From the Expert Group in Clinical and Translational Medical Research we have two strong proposals for large research infrastructures in clinical and translational medical research. The two proposals should help both the clinical and translational research in Europe and also provide new opportunities for a more successful development of the European pharmaceutical and biomedical industry.

The "Network of Distributed Infrastructures for Clinical Trials in Europe" proposal is linked to the IMI, the Innovative Medicines Initiative, a technology platform. It is further linked to networks and FP applications. The EATRIS is a three-stage proposal where the first step includes establishing five advanced centers of excellence in translational research in biomedicine. The second step comprises partnership centers in the other member states, where the five model centers will work as "role models" with strong collaborations in training, education, exchange of researchers, experts and staff and with common set-ups for clinical trials, molecular medicine, imaging, biobanks etc. The third step will involve additional EATRIS centers - with the same sharing of knowledge as in step two – across universities and hospitals in Europe. The first step with the five centers of excellence will also support interaction with EMBL, to transfer the basic science results from the EMBL laboratories into clinical practice.

The EGCT was involved in the development of the proposal on biobanks and molecular resources along with the EGGB and supports this proposal strongly. A sufficient biobanking system in Europe is mandatory to secure a future top level in clinical research. Finally, as "Imaging" proposals were part of the ESFRI "List of opportunities" and were thus relevant to the work of the EGCT, it should be noted that imaging is an integral part of both the EATRIS and Clinical Trials proposals. At the present stage, the EIRBI network is considered an emerging proposal, and is recommended for further development and inclusion on future iterations of the ESFRI Roadmap.

3.3 Biodiversity and the Environment Expert Group (BEEG)

The BEEG worked under the responsibility of the BMS RWG and was focussed on biodiversity and the environment. During seven months the BEEG evaluated seven project proposals.

The BEEG applied strict selection criteria and standard evaluation forms in order to identify mature proposals.

The selection process was based on three steps:

- Preliminary selection;

- Hearings of "interesting" proposals selected in the first step and completion of evaluation forms by all experts;

- Final selection based on completed forms, critical discussion among the members of BEEG, and on additional information requested from the authors of the selected proposals.

3.3.1 Membership of Expert Group

Professor Pieter Baas, Emeritus Professor of Systematic Botany at Leiden University, The Netherlands

Professor Birgitta Bremer, Director of the Bergius Foundation and the Bergius Botanical Garden, at the Royal Swedish Academy of Sciences (KVA) and Stockholm University (SU)

Professor Martin Gerzabek, Professor and Vice-President for Research of the University for Natural Resources and Applied Life Sciences, Vienna, Austria

Dr Terry Parr, Leader of the Ecosystem Assessment and Forecasting Section at the UK Centre for Ecology and Hydrology (CEH) Lancaster, UK

Professor Mario Tredici, Professor of Microbiology at the Faculty of Agriculture of the University of Florence, Italy

Dr Fanny Voutsinou-Taliadouri, Research Director in the Hellenic Centre for Marine Research, Greece

Professor Wolfgang Weisser, Professor for Terrestrial Ecology at the Friedrich-Schiller-University of Jena, Germany

Professor Anna Mari Walls, Director of the Center for Environmental Research, University of Turku, Finland

Jean-Baptiste Bergé (Chair until Dec 2005) Director of Research, Assistant Scientific Director, Directorate for the Environment, Cultivated and Natural Ecosystems, INRA, France

Jan Marek (Chair from Jan 2006) Secretariat of R & D Council, Prague and member of the BMS RWG

3.3.2 Methodology used by Expert Group

The methodology used by BEEG for the selection of proposals submitted it was based on the ESFRI Roadmap criteria, hearings from authors of the most promising and mature proposals and discussion among the expert members**.**

Selection was conducted in three steps:

First step: Preliminary selection and decision to merge three proposals;

Second step: hearings of promising proposals selected in the first step and completion of evaluation forms

Third step: detailed selection based on completed evaluation forms, comparison with identified strategic areas and criteria listed in the ESFRI document "Summary of the rules for making the Roadmap".

The BEEG choose to carry out a very strict final selection of proposals in order to select the most mature and competitive proposals for inclusion in the Roadmap.

3.3.2.1 First step/analysis

List of proposals evaluated in the first step

Six infrastructure proposals were initially submitted to our expert group:

- Center for Genetic Resources Preservation of Animal and Plant GERMPLASM,
- Establishment of a Resource Centre for Industrial Microorganism in the Southeastern European Countries RECIMSE,
- Infrastructure for the Analysis and Experimentation on Ecosystems (IAEE)
- European Marine Biodiversity Data System (EMBIODS),
- European Centre for Biodiversity Information (ECBIO),
- Unravelling Bio- and Eco-complexity (an up-dated extended version of this proposal has also been submitted entitled "Biodiversity databases and observatories for European Research" (EU-BIODOBS).

Additionally the BEEG received from the BMS RWG three other proposals that were evaluated in the same way.

- European Marine Biological Resource Centre,
- Global service Platform on Sustainable Management and Enhancement of Agro-Ecosystems in the Mediterranean (PLASMED),
- An Integrated Carbon Observation System (ICOS),
- Integration of routine Aircraft measurements into a Global Observing System – a European Research Infrastructure (IAGOS-ERI).

Criteria

"Criteria for Entering the Roadmap Process" were used for the first step selection.

- Major infrastructure for the particular scientific community
- Multi-user facility
- Pan-European interest
- Programme agreed by the appropriate community
- Technological feasibility
- Multi-annual funding
- Maturity based on appropriate science case, technical case and business case

The evaluated proposals were initially ranked into two categories:

(1) Considered "immature" or beyond the expertise of BEEG

- GERMPLASM, RECIMSE, "European Marine Biological Resource Centre" and PLASMED were evaluated as immature and without sufficient pan-European interest. It was not considered useful to ask for additional information at this stage,

- The proposal IAGOS-ERI, which was submitted to BEEG by EMEG, was after a short discussion sent back to EMEG without comments because our group lacked the appropriate expertise.

- The project ICOS that was primarily evaluated by the Environmental Monitoring Expert Group (EMEG) set up by the PES RWG where it was considered interesting, was discussed and considered to be of great potential.

(2) Considered "interesting", which could enter the roadmap

- Infrastructure for the Analysis and Experimentation on Ecosystems (IAEE),

- European Marine Biodiversity Data System (EMBIODS), European Centre for Biodiversity Information (ECBIO) and Unravelling Bio- and Eco-complexity. The chairperson contacted the coordinators of these three proposals and asked them to merge all three infrastructure proposals into one single proposal. An up-dated extended version named "Biodiversity databases and observatories for European Research" (EU-BIODOBS) was subsequently submitted to the BEEG.

The coordinators of IAEE and EU-BIODOBS were invited for a hearing at the BEEG meeting. The BEEG also considered recommendations from the Scientific Committee on Agricultural Research (SCAR).

3.3.2.2 Second step/analysis

In the second step two hearings were organised; authors of both ANAEE [former IAEE] and EU-BIODOBS were invited to present their project proposals, and both were subsequently evaluated in detail.

Speakers were asked for detailed information concerning relevance to other existing and developing international facilities, estimated construction, operating and decomissioning costs, management structure, impact on human capacity and training and potential contribution to other socio-economic objectives.

Thereafter members of BEEG were asked to fill in the evaluation forms. No selection was made in the second step.

3.3.2.3 Third step/analysis

In the third step only two proposals were evaluated: ANAEE and LIFE-WATCH [former EU-BIODOBS]. The final selection made in the third step was based on

(1) Evaluation forms completed by experts of BEEG;

(2) Comparison of both proposals with strategic areas: [1] Status, trends and distribution of habitats and species of Community interest; [2] Impacts of pressure on biodiversity for each key sector; [3] Tools for measuring, forecasting and improving the most important policy instruments for sustainable use of biodiversity in each of the sectors.

(3) Comparison of both proposals with rules mentioned by ESFRI for making the Roadmap: [1] scientific case and corresponding to priority needs of the scientific communities in Europe, [2] maturity of proposal based on technical and business case including costs and [3] the mechanisms for other partners to join later on.

3.3.3 Conclusions/Overview of Proposed Infrastructures

Based on the methodology mentioned above the BEEG concluded that

- The proposal LIFE-WATCH [formerly EU-BIODOBS] is mature and is strongly recommended by BEEG to be included in the Roadmap.

- The proposal "Infrastructure for the Analysis and Experimentation on Ecosystems" [ANAEE; former IAEE] is a good emerging project. After improvement of the sections "Management", "Costs", and "Partnership", the BEEG recommends it for reconsideration as a Roadmap infrastructure.

Rationale

Without an underpinning, distributed site- and collection-based infrastructure for biodiversity science, Europe will fly blind in its attempt to stop biodiversity loss or to use its components sustainably, both within its own borders and in the developing world where high biodiversity levels are most at risk. The **LIFE-WATCH** infrastructure proposal precisely addresses these needs. It will open new ways for high quality research of global relevance. By integrating the communities of three Networks of Excellence (NoE) and through its open nature the role of LIFE-WATCH in existing landscape is positive. The LIFE–WATCH proposal meets the first and third strategic areas identified by BEEG and responds to the needs of the European science community dealing with biodiversity and the environment. LIFE–WATCH has a detailed scientific concept, with a well-elaborated technical, feasibility, management and reliable financial aspects and with known partnership. LIFE-WATCH allows open access of the European scientific community to all collated data. The potential user community is very broad due to the immense fields covered and thanks to open access to data sets and services. Support for LIFE-WATCH has been expressed by the organisations participating in the current FP6 NoEs. Financial aspects are well underpinned by background information.

The ANAEE project proposal is considered well elaborated from a scientific point of view. Its potential role in the existing landscape is considered quite positive and the ANAEE project meets the second strategic area described in Part 5 of this report (see Emerging Proposals and ANAEE). Nevertheless, the BEEG is of the opinion that it is unclear if there are any sufficiently committed partners behind the proposal (i.e. support by several institutions from several countries) and that the project appears to be focussed around one specific facility. The technical and technological case is not well developed and the proposal can be seen as a preliminary concept rather than a detailed scientific plan because some vital information is missing like timetable, deliverability or implementation plan, commitments of different stakeholders, training etc. Financial aspects are also considered inadequate in this moment. The project proposal needs to be developed further concerning these aspects in order for it to be recommended for inclusion on the Roadmap.

3. Recommended Proposals for New and Upgraded Research Infrastructure

1. Name and descriptive title

Bioinformatics Infrastructure for Europe

2. Short description of new RI (or major upgrade) and main characteristics

The world's body of bioinformatic data is a critical input for all biological and biomedical sciences and all life-science based industries. The proposed infrastructure will ensure free provision of this essential input to the entire scientific community. It will encompass an interlinked collection of robust and well-structured and evaluated core databases, capable of accommodating the ongoing massive accumulation and diversification of data pertinent to the biologist. It will permit the integration and interoperability of diverse, heterogeneous, potentially redundant information that is essential to generate and utilise biomedical knowledge. It will encompass the necessary major computer infrastructure to store and organise this data in a way suitable for rapid search and access, and will provide a sophisticated but user-friendly portal for users. It will be embedded in a database-related research programme that supports the development of critically important standards, ontologies and novel information resources. It will also link to distributed organism specific knowledge resources and, as appropriate, to speciality and emerging databases of wide interest (e.g. image collections). It will represent a secure but rapidly evolving platform for data collection, storage, annotation, validation, dissemination and utilisation, consistent with the unique requirements of shared resources in the life sciences.

The proposed infrastructure is based around a substantial upgrade to the existing European Bioinformatics Institute (EBI) to allow these objectives to be met. Primary data resources are now so large and growing so rapidly that handling them in one place is most appropriate. Secondary data resources, that organise and annotate these primary resources to add value to them, are distributed across Europe and make the most of the diverse expertise of its scientists. The proposal seeks to ensure that valuable secondary resources are stably supported and that the entire collection of resources is well integrated to generate and utilise knowledge in the life sciences.

3. Science case (scientific justification, including new areas to be opened)

Bioinformatics resources are and will remain a universal requirement for the life sciences, even more so in the current era of high-throughput (HTP) data collection in genomics, proteomics etc. and requirements for large scale integrated analysis, for example for systems biology. Databases are typically the only record of HTP science, and are irreplaceable for accessing the entire, rapidly evolving corpus of biomolecular information, from the molecular to the organism level. New categories of data are emerging, e.g. three-dimensional dynamic images, HTP mass spectrometric proteome identification, phenotypic and physiological data, polymorphism and chemo genomic data. Linking information from biobank collections with medical records in a standardised way, using ontologies, will also be of major importance for medical and pharmaceutical developments.

The productivity of biological and biomedical sciences and related industries are increasingly dependent on the ease of access to this entire body of data. The value of the HTP data that is being collected far exceeds the cost of storing and providing access to it, however investment in infrastructure has not kept pace with

the very rapid rate of data growth.

One of the oldest data resources can be considered as an example of the need for continuous upgrades of infrastructure. DNA sequence records are stored in the EMBL database, which has existed for more than 20 years. This database, housed at EBI, is part of a 3 way international agreement with Genbank (US) and DDBJ (Japan). The size of this database has grown exponentially since its inception. From the 1980's to mid 1990's (when genome sequencing started in earnest) the database doubled in size every 23 months. From the mid 1990's the rate of growth had increased such that the database doubled every 16 months. Despite the completion of the human genome, this doubling rate has been maintained. Recently a sister database has been established for unassembled DNA sequence (The Trace Repository) to handle the growth in data collected in this form, also as an international collaboration with the US. This database already contains 1 billion records and is doubling every 11 months. At 22 Terabytes the database is already one of the largest single scientific database in the world. It can be predicted with confidence that, within a decade, bioinformatics requirements will be comparable with the computational requirements of the physical sciences. New technologies are likely to drop sequencing costs by several orders of magnitude in the next decade. This will drive the collection of sequence data on a new scale as it will become cheap enough to be used as a routine screen in human genetics research. While it is anticipated that in future these databases will grow even faster, the current doubling rate of every 11 months is already faster than the 'Moore's law' growth of both computer disk storage and CPU speeds. The effect of such high growth rates is that computer infrastructure to support such resources must grow physically even if it is being upgraded continuously.

Although support for the EMBL database has been sufficient to keep up with storing the raw data submitted to it, it has not been sufficient to keep up with the work required to optimally organise, annotate or provide services based on this data. The setting up of a European Trace Repository for raw sequence data was only possible at all through the cost being underwritten by the Wellcome Trust at the Sanger Institute. By contrast the US partner of these international collaborative data resources, NCBI (National Centre for Biotechnology Information), has been substantially better funded (appearing as a line item in the congressional budget) and has since the 1980's dominated world bioinformatics data services, with well supported services such as Blast, Entrez and PubMed.

For other more complex forms of biological data such as transcription expression array data (The ArrayExpress Database at EBI) there is potentially an even larger gap between the level of support provided and what is realistically required to maximise the value of this data. As a result of this under funding, ArrayExpress has been losing its initial technology lead to the US based competitor resource GEO at NCBI. Another European reference database UniProt (formally SwissProt) was unable to find sufficient support for even its primary activities and became semi-private in the 1990's. The negative effect of commercial restrictions on data sharing and integration of bioinformatics resources resulting from this arrangement was so severe that in 2002 the US National Institutes of Health (NIH) decided to fund UniProt to return it to the public domain. While the ability of UniProt to attract NIH funding is a strong confirmation of its international standing, there should be some concern that as a result NIH has gained some rights over one of Europe's most prestigious database resources.

The requirements to support bioinformatics infrastructure are therefore twofold. Firstly computer infrastructure must be continuously upgraded to keep pace with data growth. Secondly adequate personnel must be supported to handle this data to maximise its value. Our experience of handling biological data is that organising captured data into an exchangeable archival format is very difficult. However the effort is worthwhile as when data is organised optimally it creates very powerful resources. There is a significant personnel requirement for the continuous construction of bioinformatics resources. This includes personnel for software development for databases and external portals to the data, but also personnel to manage, curate and where appropriate add annotation to the data. This process of capturing data about biological systems has only just started and is expected to scale rapidly with new categories of data from new types of HTP experiment, so European bioinformatics infrastructure needs to scale similarly.

This infrastructure proposal will create a stable foundation for data collection, storage, annotation and distribution to address this. The speed of internet access coupled with the unwieldy size of primary databases mean that database replication to multiple European centres from a single hub is no longer

justified in most cases. EBI is already the recognised hub for bioinformatics in Europe and it is appropriate that the large scale infrastructure of the proposal is located there. Given that much of bioinformatics analysis on primary data resources is centred around searching across entire datasets, it is appropriate to centralise the data storage and compute resources. However, to ensure the most internationally competitive bioinformatics tools and services are developed, it is essential that primary repositories are required to provide efficient programmatic access (Application Programming Interfaces - APIs) to their data to allow bioinformatics centres across Europe to build services on top of them. This will be ensured through a strong emphasis on the development of interoperable data standards and their robust implementation. Such standards will enable unhindered development of tools and analysis by European bioinformaticians and maximise the value of bioinformatics for biological and biomedical sciences and related industries. Associated with this will be the development and adoption of common European protocols for the timely release and sharing of data and tools developed with public funds

4. The Concept case (maturity of proposal)

Europe has a well established bioinformatics infrastructure centred around data resources provided by the EBI. Primary repository databases and associated standards for data representation and annotation are well established for some data types (e.g. DNA and protein sequence, protein structure) although relatively new for others (e.g. microarrays, proteomics, imaging). Some are part of global repository structures to divide the huge task of data collection and validation and ensure redundancy of these irreplaceable primary collections, security of access, validated interoperability etc. There are a large number of secondary data resources integrating experimental observations and adding annotation to organise the primary data (e.g. protein family, pathway, interaction, model organism, genome annotation) varying from established resources that are widely used and critical to research, to specialist resources restricted to subsets of data, to research projects that explore novel ways of analysing, integrating data and providing tools to access it.

Given the growth in data scale and complexity it is essential that data resources have sufficient support both to continuously increase capacity while maintaining existing production systems and improving data validation, representation and integration in parallel. Few data resources in Europe are supported at this level. The major limitation on European bioinformatics resources reaching their potential is the lack of adequate and stable support. This proposal would allow existing activities to be rapidly scaled to a point where there is sufficient resource to allow substantial proactive innovation beyond keeping up with the flow of raw data.

To evolve a bioinformatics infrastructure for Europe of the proper scale requires a total funding of approximately €600 million over 7 years. Existing support for the resource component of EBI is about 21 M€ per year. Support for EBI needs to more than double to address both data growth and to put European bioinformatics infrastructure on a sound footing. Beyond the primary databases based at EBI and its partners there are a significant number of core secondary data resources that provide repositories of smaller collections of HTP data, archival annotation and integration of primary resources. Together these make up the core bioinformatics infrastructure widely used today. It is proposed that 70 per cent of this proposal would support EBI resource activities and 30 per cent would be targeted to support other primary and core secondary data resources.

The proposal consists of the following components:

Preparatory costs: 80 M€ (30 M€ + 7 M€ per year)

To address the anticipated rates of data growth, substantial continuous upgrading of computer infrastructure will be required, the largest part of which will be concentrated at EBI. EBI lacks a data centre capable of accommodating any such increase. It is proposed that a 1000 m^2 data centre with high capacity cooling is built in the first year at EBI to accommodate current and future needs. Such a facility would cost about 30M€ to construct.

The value of biological data is increased if it can be collected in standardised formats with appropriate

metadata. Experience with the development of standards, such as the MIAME standard for microarray data, shows that substantial effort is required. The proposal therefore includes 7 M€ per year (50 M€ total) to support standards development work. This should ensure a more rapid response to new data types, through proactive rather than reactive development to accommodate them. This support should involve prototyping of database systems and services, engagement with data generators to collect pilot datasets and engagement with the user community to ensure standards for collection and dissemination capture the required aspects of the data type.

Construction costs: 470 M€ (67 M€ per year)

Continuous upgrades are required together with a rolling program of computer upgrades to keep pace with data growth. Construction of databases is a continuous process of importing, and organising new and disparate biological data and development of database structures, APIs to allow programmatic access and user friendly portals. Of the 67 M€ support per year, 25 M€ would be on computer system, associated network hardware, software etc., the vast majority of which would be located at EBI.

Operation costs: 50 M€ (7 M€ per year)

Operations costs for bioinformatics resources are limited to systems administration of computers providing online services and associated network and utility costs.

Decommissioning costs: 100 M€

The value of archived data warrants its continuous availability, so if a decision was made to decommission any existing facilities, replacement facilities elsewhere would need to be 'recommissioned'. The worse case cost would be the 'recommissioning' of the whole of EBI, which would be cost at least 100 M€ for a new data centre and other facilities to be constructed.

All of the above components, except the data centre, will be split between supporting activities at EBI (70 per cent) and at other primary and core secondary data resources (30 per cent). Since the development, scaling and in some cases merging and evolving of existing resources takes place rapidly, it might be appropriate for the distribution of development funds to databases outside the EBI to be handled through a committee of external experts supported by a small secretariat, in charge of a pluri annual financing scheme of the infrastructure (4 years budget with a midterm evaluation). The secretariat should be sufficiently resourced to develop criteria to assess usage, impact and integration of different data resources so as to be able to advise the committee and make recommendations about the appropriate level of support.

5. Further information, including strategic importance to ERA

It is widely recognised that appropriate use of bioinformatics can increase research efficiency by identifying potential functional relationships, new targets etc. much faster than can be done by experiment. While hypotheses require experimental investigation, bioinformatics can be used to substantially filter the list of candidate experiments resulting in faster outcomes. Due to a long period of limited support, existing bioinformatics services are currently inadequately integrated, developed or used in Europe. Greater and more sophisticated use of existing data would lead to a substantial increase in productivity and competitiveness in biomedicine across Europe. This infrastructure initiative will provide the level of core infrastructure to allow bioinformatics to meet its potential. A number of the existing primary data resources are embedded in tri-continental collaborations for data exchange and free access. Up to now these efforts have been disproportionately supported by US funders, making the US a magnet for bioinformatics innovation and in turn leading to more mature use of bioinformatics within US biology as a whole. This proposal will allow Europe to leverage off these international relationships while having sufficient resource to fully exploit and drive future developments.

6. Identification of other socio-economic impacts

The envisioned infrastructure for biomedical data is crucially important to academic and commercial research, including basic biology, medicine, pharmaceutical, agricultural, nutritional and environmental science. By boldly developing, upgrading or linking the proposed data resources, Europe is capable of establishing infrastructure facilities second to none which, together with ancillary research and training, will enable Europe-wide, world-leading biomedical research and industrial development. Major life science projects are ongoing through private sector, Member State and EC funding. Bioinformatics represents one of the largest leverage factors, by permitting full use of data that collectively are costing many billion euro. Such an integrated bioinformatics infrastructure would be a key contribution to the achievement of the Lisbon objectives.

7. Participating organisations / support from Member states

The infrastructure proposal is centred on the EBI however there are primary and core secondary data resources located at other centres where data growth rates require that they be supported explicitly under this proposal. Major centres and their primary data resources are:

EBI (European Bioinformatics Institute):

EMBL DNA database*; UniProt*; eMSD* ArrayExpress, IntAct etc.

SIB (Swiss Institute of Bioinformatics)

UniProt*

WTSI (Wellcome Trust Sanger Institute)

DNA trace archive*

* part of international (bi or tri-continental) collaborations

EBI infrastructure activities are currently substantially supported through EMBL (~50 per cent) and through funding from US NIH, Wellcome Trust and UK research councils (~25 per cent) and EU (~25 per cent). EMBL is itself supported by national research councils of 19 States, 14 of which are EU member states. Of the remaining states, 2 are members of EFTA, 1 of EEA and 1 is a candidate accession country. Although recent support for EBI through EU grants has been substantial, it is widely recognised that its activities are still substantially under funded and unstable.

There are a large number of valuable secondary data resources located at universities and institutes across Europe. Most are linked to EBI resources and very many have formal collaborations with EBI. The funding of most is highly unstable and depends on research councils bending their own rules and approving grants that are substantially infrastructure provision rather than basic science. When grants are rejected websites and databases stop being maintained, services quickly fail and valuable data that has been collected and curated over many years can be lost. To address this, while 70 per cent of this infrastructure proposal would support the large scale data resources at EBI, 30 per cent would be targeted to support other primary and core secondary data resources.

8. Budgetary information

Preparatory cost (total in M€)	Construction cost (total in M€)	Operation cost (total)	Decommissioning cost (total in M€)
80	470	50	Not applicable

30M€ in 1st year for a new 1000 m^2 data centre building to accommodate computer systems. 50M€ over life time of funding for preparatory development biological data standards.	Continuous upgrades are required together with a rolling program of computer upgrades to keep pace with data growth. Construction of databases is a continuous process of importing and organising disparate biological data, as is development of database structures and API software	Systems administration of computers providing online services and associated network and utility costs.	The value of archived data warrants its continuous availability, so if a decision was made to decommission existing facilities, replacement facilities elsewhere would need to be 'recommissioned'. Recommissioning the entire EBI would cost at least 100 M€.
(of which likely to be obtained by possible stakeholders) 32	(of which likely to be obtained by possible stakeholders) 235	(of which likely to be obtained by possible stakeholders) 50	(of which likely to be obtained by possible stakeholders)

9. Timetable until operation

Give a short estimation about the timetable until operation

Preparatory phase	Construction phase	Operation	Decommissioning
Years 1-7 (see above)	Years 1-7	Years 1-7	Not applicable

10. Contact

Professor Janet Thornton
Director
European Bioinformatics Institute
Wellcome Trust Genome Campus
Hinxton, Cambridgeshire, CB10 1SD, UK.
thornton@ebi.ac.uk
(Institute Director)

http://www.ebi.ac.uk/

1. Name and descriptive title

Integrated Structural Biology Infrastructure for Europe

2. Short description of new RI (or major upgrade) and main characteristics

One of the grand challenges in biology is to combine *integrated structural biology* with cell biology so that an atomic level dissection of the cell can be reconstituted into a functional system (**3D cellular structural biology**). A major aim of this infrastructure is to move structural biology from the study of single protein molecules to the study of the more complex systems used by cells with the long-term aim of using structural biology, together with cell and systems biology to be able to describe in detail how a cell functions. New tools will have to be developed to understand the complexity of the molecular networks and processes on which cells depend. It is essential to include a temporal component in such studies.

The ***Integrated Structural Biology Infrastructure Project*** will provide a central framework for 21st century biology and pharmaceuticals. At this early stage much of the work must be at the level of providing an understanding of the structure and dynamics of individual proteins, protein complexes and how they control fundamental cellular processes. This will be achieved, in some cases using model systems, by close linkage with medical and biological research, as far as possible focused on human health, such as cancer, infectious diseases and host-pathogen interactions, and/or environmental problems, such as adaptation of life to extreme conditions of temperature, heavy metals, radiation and toxic molecules.

This grand challenge will be addressed by building a pan-European infrastructure of distributed ***Integrated Structural Biology*** **Centres**, linked into **a network**. The Centres will combine excellence in structural biology with specific technologic and developmental tasks. The Centres will be chosen on the basis of their complementarities and the strength of existing infrastructure, taking into account originality, the importance of the biological questions being addressed and the relevance to European priorities, such as human health, the environment, therapeutic innovation and biotechnologies. The Centres will be open to the European academic and industrial world and will provide, on a project basis, access to production and experimental facilities. The services will include expertise, key advanced technologies, as well as support for innovation.

The Centres will develop complementary expertise and infrastructures depending on their focus areas, but all will maintain a set of core technologies. In the wet-lab these must include protein/macromolecular complex production using parallel technologies as well as the generation of organelles, cellular samples and functional characterization. In the dry lab these will include NMR, X-ray and electron crystallography, cryo-EM and tomography, plus electron, scanning probe and different forms of light microscopy. Each Centre will have a specific biological focus (e.g. viruses, membrane proteins, ion channels, large transient complexes, enzymes, filamentous proteins) that will drive the development of front rank technological and methodological expertise, notably for production and analysis of functional complexes.

The network will be organized as a pan-European infrastructure with a central scientific and financial management coordinating the centres activity (see part 4).

The proposed infrastructure will:

- provide the combination of cutting edge technologies acting in different resolution - ranges appropriate to each of the required scales and bridging the gaps between them,

- innovate and develop new approaches and technologies for structural biology and ''3D cellular biology''. This will provide opportunities for interdisciplinary research,

- coordinate links between the different pre-existing large scale infrastructures already developed in Europe for data acquisition (synchrotron and neutron sources, NMR facilities),

- identify major scientific questions to drive and focus the research of the Centres and the technological innovation in a European biological and biomedical framework, and address the relevant bottlenecks,

- provide and coordinate training in 3-D Integrative Structural Biology

- provide links to the physics, information sciences and engineering sciences communities at a unique level of integration in Europe.

A second level will be built by a number of laboratories and facilities that will be closely connected to those of the first level, and will be those mainly involved in offering easy access to users all across Europe. To guarantee the dissemination of excellence all across Europe, the regional distribution of these second level facilities would be carefully planned.

3. Science case (scientific justification, including new areas to be opened)

The network of Centres and Nodes will be organized in order to obtain multi-scale structural data and translate these data into functional knowledge, which will provide essential underpinning knowledge for health and biotechnology innovations. The need for this integration is that the cell operates through the action and interaction of large macromolecular complexes, which in some cases are relatively stable (eg ribosomes) and in other cases transient (e.g. spliceosomes). Understanding the functioning of the cell requires not only a definition of the networks of interactions through systems biology, but also defining the nature of the information and agents of information transfer (what does this mean?) within the system, which can only be fully defined at the level of dynamic structures through cell biological studies. The temporal component is crucial and to reconstitute the proper sequence of events several snapshots will be necessary making the overall project a formidable task.

The technical developments in each of the major techniques (production and functional screening of macromolecular complexes, EM tomography and cellular imaging, solution and solid state NMR etc) will be championed by a few of the associated Centres while certain additional methods, including X-ray and neutron non-crystalline diffraction, X-ray microscopy and coherence imaging, will be available at least at one specialist Centre. It will also be necessary to develop the mathematical methodologies to combine the resulting information. Innovative chemistry and biology for the design of molecular markers as well as of molecules that activate or lock transitions of transient complexes will also be required.

This proposal synergises with the planned development at the European level of infrastructures for data and information management. The relationship between bioinformatics and structural biology is symbiotic and a concerted European plan of action for both is required. Similarly light and neutron sources as well as NMR large scale facilities, and the associated instrument developments including design studies for new technologies in the field of NMR are already supported by EU programs within the sixth framework. These new high throughput facilities cannot be fully exploited unless biological samples can be provided. For that goal a European commitment to develop structural biology Centres focused on the most challenging biological questions is required. Such a commitment would also build on recent developments in imaging which offer the real possibility of bridging between the molecular and cellular levels and provide the infrastructure to further develop the methods and extend them at 3rd and 4th generation light sources. Importantly, the *integrated structural biology infrastructure* should also foster outreach to the nanotechnology community.

The X-ray free electron laser (XFEL) planned in Hamburg is a good illustration of potential breakthroughs which may allow "filming of chemical reactions, direct mapping of the atomic details of molecules as well as capturing 3D pictures of the nanocosmos." This ambitious development is expected to be ready for testing of

biological applications in 2012. The experimental phase of the evaluation in structural biology, notably the design of experiments and the preparation of adequate samples, will be programmed for the first funding period while implementation of research programs will become increasingly important in the second period.

The proposed infrastructure will provide a decisive competitive advantage for drug and vaccine design in connection with development of new therapies and diagnostics by pharmaceutical and biotechnological companies.

4. The Concept case (maturity of proposal)

The scientific community is large and well structured as witnessed by the ESF list of European macromolecular crystallographers (http://www.weizmann.ac.il/esf_xtal), which contains several thousand scientists, and by the fact that 15 structural biology projects are currently supported by the EC. In the area of structural biology European scientists are the global leaders, and the strength of this area is highlighted by the 13 Nobel Laureates which since 1960 have emerged from the European structural biology community. The existing infrastructures include EMBL outstations both at the DESY-Hamburg and ESRF-Grenoble Synchrotrons and several other significant centres. Moreover, the Forum for European Structural Proteomics, FESP, has been established to assess infrastructures and define a long-term EU strategy for structural biology (http://www.ec-fesp.org).

The strength of structural biology in Europe has been recognised by the national funding bodies and by the EC with the funding of large scale networks and integrated programmes in the 5th and 6th frameworks (e.g. SPINE, BIOXHIT, 3-D REPERTOIRE, E-MEP, VIZIER) as well as infrastructures (synchrotrons and NMR large scale facilities). These have successfully maintained Europe at an internationally competitive level, and as a result there is already an established basis for networking and cooperation at the pan-European level. However these projects are strictly time limited and unless there is a coherent plan to build on the successes then the full value of the investment will not be realised. The completion of the 6th framework projects defines the timescale of the current proposal.

The present project is the rational counterpart to existing (synchrotrons and neutron sources as well as NMR large scale facilities) and planned investments (XFEL) for structural biology in Europe on the Very Large Infrastructures of Physics. Indeed the huge effort in Europe centred on Synchrotron facilities (BESSY, DESY, DIAMOND, ESRF, LUCIA, PETRA, SCANDINAVIA, SLS, SOLEIL, TRIESTE), neutron sources (ILL, ISIS, SNeutronsS and Julich) and continued investment in high field NMR spectrometers (850-900 MHz instruments currently available in Berlin, Florence, Frankfurt, Göttingen, Lyon, Munich, Utrecht and projects are being developed toward 1 000 MHz machines) would be strongly legitimised by the existence of a European network of *integrated structural biology* infrastructures.

These centres would also develop and take advantage of synergies with other life sciences infrastructures (e.g. bio-computing, systems biology) and dedicated large scale infrastructures i.e. functional genomics centres, sequencing centres.

We propose an **infrastructure for *integrated structural biology*** in Europe consisting of distributed centres with a pooled budget. The network will be organized as a pan-European infrastructure with a central scientific and financial management coordinating the centres´ activity. Each Centre will nominate a structural biologist to serve on the management board. Board meeting will be held regularly (i.e. monthly) physically or through videoconferences. This procedure has been successfully implemented in other integrated consortia (e.g. Structural Genomics Toronto-Oxford-Stockholm).

A list of potential sites that would meet the criteria of specific expertise with existing support might include but is not limited to: Munich (EM), Florence (NMR) and Utrecht (NMR), Grenoble (synchrotron), Hamburg (synchrotron, XFEL), Oxford (synchrotron and biomedical research), Strasbourg (functional genomics and biomedical research), Göttingen (NMR, spliceosomes), Frankfurt (membrane proteins) Other sites with specific expertises could be selected to strengthen the network, notably in Nordic or new Member States.

In order to build and/or maintain this network of state-of-the-art facilities for *integrated structural biology*, the operational budget over 7 years will be of the order of 425 M€. This total figure is based on the following.

Preparatory costs : 50 M€

Pilot project : upgrade of some centres with high end equipment for key technologies.

Training and management

Construction costs : 250 M€

Building/Refurbishment: distributed among the successful applicants according to need in this area.

Equipment: Each Centre will need to be equipped with the High Throughput core tools of structural biology, equipment (X-Ray diffraction equipment, NMR and mass spectrometers, electron microscopes i.e. FEG cryomicroscope) together with robotized facilities for biomacromolecule production, purification and crystallization. Equipment on top of the existing equipment will be available just for the biological focus area the Centre specializes in. Depending on its specificity and scientific themes each Centre should be equipped with general and more specialized techniques for instance in biophysics (light scattering, analytical ultracentrifugation, circular dichroïsm, calorimetry, fluorescence, kinetic data and single molecule spectroscopies, etc) and imaging for cellular analysis (scanning probe, modern optical, or electron microscopies and tomographies). Centres will already possess much of this equipment so that the new funds can be used to equip and update the Centre for the core technologies necessary for the biological area in which the Centre will specialise.

NMR spectrometers: The new (1000 MHz and beyond) generation of spectrometers are expected to cost up to 10 M€ each. This exceeds the budgetary capabilities of almost all national funding organisations. It is suggested that this proposal should include 40 M€ in special funding to be awarded competitively to provide such high field spectrometers. These could be located at Centres concerned with advancing NMR techniques for Angstrom microscopy or at specialised NMR laboratories close to such Centres.

Operation costs : 125 M€

- R & D: A significant part of the global budget will be dedicated to innovation and setting up new technologies.

- Running costs: (consumables, travel and accommodation expenses for visiting scientists, maintenance at 10 per cent of total equipment value per year)

5. Further information, including strategic importance to ERA

Structural biology traditionally belongs to Big Science in terms of its infrastructure requirements and these should be organized following the rules of other large-scale facilities.

Although Europe has played a leading role in the development of structural biology since its foundation in the 1950s, the infrastructure required for research in *integrated structural biology* is only partially developed at the European level. Very few sites have the breadth of technologies necessary to propose an integrated structural analysis that combines atomic structure determination with functional cellular context. Equally importantly within the European academic funding structure few if any sites can sustain a long term effort at the cutting edge of *integrated structural biology* if funding comes only from national sources.

The investment proposed here is comparable to those already implemented in the US (NIH road map for structural biology high throughput structural determination facilities etc) and Japan (for instance the Protein 3000 and CoE programmes). Such investment is unavoidable if Europe, where the foundations of structural

biology were established, is to contribute at a major level to the challenge of understanding cellular complexity at an atomic level.

6. Identification of other socio-economic impacts

6.1 Human health and environment

There is now an enormous potential for structural biology to contribute to post-genomic biomedical research. Both normal and pathological protein-based mechanisms are potential targets for therapeutic intervention. Structure-based development of therapeutics is already integrated into the pharmaceutical industry, (e.g. firms set up to develop new antibiotics based on ribosome coordinates) however, academic research has the potential to identify, for instance, new targets for cancer therapy, antibiotics and antivirals and to demonstrate proof of principle for more innovative, non active-site directed compounds. There is also an urgent need to put vaccine design on a sound structural foundation. Finally there are numerous possible environmental applications, for instance the structure-based design of microorganisms and plants that are able to cleanse the soil of toxic metals.

6.2 New technologies and innovation

To understand cellular processes at an atomic level technological development will be required to bridge between the atomic perspective of X-ray crystallography or NMR spectroscopy and the cellular context addressable at lower resolution by technologies such as cryoelectron microscopy, optical and multi-photonic microscopy. Since complexity is the essence of life very large quantities of data will need to be collected from native, pathological or engineered systems. In terms of logistics this means production and handling of samples using less biological and chemical material in a high throughput scenario. These demands will necessitate the development, in addition to improved instrumentation that decreases the necessary amounts of material, of new technologies for sample and cell preparation and characterisation. Such developments will only be possible through radical ‘’innovation’’ involving micro-fluidic systems and nano-devices. At present the European contribution to these developments remains limited. The tools produced will be of fundamental value not only for clinical approaches, but also for biotechnology at large.

6.3 Industrial impact

The impact on industry will be twofold. The requirements in, for example, miniaturisation and higher precision instrumentation, will challenge European industry to advance their technological capabilities. Conversely, the use of the infrastructure by the industrial sector, plus the information generated using these facilities by the academic sector, will strengthen the competitiveness of Europe based biotechnology, bioengineering and pharmaceutical companies and lead to new and profitable commercial products.

6.4 Training

Structural biology is entering a new era with challenges of increasing complexity. To equip European researchers to respond at an internationally competitive level in this fast developing world the project will include a training program based on the latest innovations in relevant interdisciplinary expertise from biology, chemistry and physics. The training program will be open to all partners academic and non academic, i.e. to both PhD students and researchers.

7. Participating organisations / support from Member states

The potential centers are well established strong sites already supported by their national/international organisations (i.e. : MRC, BBSRC, Wellcome Trust (UK), CNR, Ministry of Research (Italy), Helmholtz Society, Max Planck Society and Federal Länder (Germany), CNRS, INSERM, Ministry of Research and Education

(France), NOW-CW (Netherlands) and EMBL

8. Budgetary information

Preparatory cost (total in M€)	Construction cost (total in M€)	Operation cost (total)	Decommissioning cost (total in M€)
50	250	125	/
(of which likely to be obtained by possible stakeholders)	(of which likely to be obtained by possible stakeholders)	(of which likely to be obtained by possible stakeholders)	(of which likely to be obtained by possible stakeholders)
20	180	90	/

9. Timetable until operation

Give a short estimation about the timetable until operation

Preparatory phase	Construction phase	Operation	Decommissioning
3 years (2007-2009)	4 years (2010-2013)	6 years (2008-2013)	/

10. Contact

Give the reference of the coordination organisation and contact person; whenever possible indicate web site(s) of reference.

SPINE Coordinator
Pr. David STUART, Ph.D.,
University of Oxford, Division of Structural Biology,
the Henry Wellcome Building for Genomic Medicine,
Roosevelt Drive, Headington, Oxford OX3 7BN, UK

e-mail: dave@strubi.ox.ac.uk

http://www.strubi.ox.ac.uk/

1. Name and descriptive title

INFRAFRONTIER - Functional Genomics in the Mouse as a Model of Human Disease

2. Short description of new RI (or major upgrade) and main characteristics

The fields of functional genomics, medically related life sciences and systems biology use the mouse as a model system to understand the molecular basis of health and disease in man. In the coming decade, saturation mutagenesis in the mouse will be one of the major tasks of the scientific community and will require a dramatic change in the way of phenotyping and archiving of mouse models. Infrafrontier will organise two complementary and linked European infrastructure networks for large scale and comprehensive phenotyping (Phenomefrontier) and archiving (Archivefrontier) of mouse models. Infrafrontier will be embedded in a global effort to standardise and optimise the phenotypic characterisation of medically relevant models and in addition state of the art archiving and dissemination of such. Thus, Infrafrontier will provide the umbrella of a pan-European effort to standardise and optimise the phenotypic characterisation of medically relevant mouse models and a state of the art archiving and dissemination of such important biological samples.

The international collaboration over the three continents - Europe, America and Asia, is crucial (see Appendix I, II and III). As far as Phenomefrontier is concerned various levels of operations can be envisaged: a) large mouse clinics; b) topic-based phenotyping laboratories, where special research problems can be analysed and phenotyping deepened; c) individual laboratories that interact with the clinics and the topic-based laboratories. Infrafrontier will also provide the scientific community with training courses and other initiatives in order to promote the handling of experimental animals in a professional way.

As far as possible problems that may arise, concerning the interpretation of Intellectual Property Rights, there should be an attempt to formulate an international agreement.

3. Science case (scientific justification, including new areas to be opened)

There is consistent evidence for the conservation of molecular and cellular mechanisms between mouse and man. Furthermore, the availability and continuous development of unique classical, together with reverse genetics technologies applied in mice have provided to the scientific community the model of choice for the analysis of the human system in physiological and pathophysiological circumstances. Infrafrontier, which consists of Phenomefrontier and Archivefrontier, will be the European platform to make best use of mouse models for the understanding of molecular and cellular networks underlying human health and disease. Infrafrontier will enable European Laboratories to make effective use of such mammalian models in the global effort to understand the logic of construction and functioning of complex systems.

Phenomefrontier. It can be envisioned that within the next decade over 25000 new mouse models will be generated in Europe. It will be necessary that this large number get access to comprehensive functional and molecular characterization. Phenomefrontier will provide a European platform, which will give access to comprehensive phenotyping to every laboratory including latest *in vivo* imaging technology and informatics tools to handle the phenotype data. Phenomefrontier is a program that aims to play a leading role on the worldwide level.

Archivefrontier. To make full use of mouse models it will be essential to make them accessible to every laboratory in Europe. Archiving and distribution of mouse models under highest quality standards and dissemination of knowledge are the main topics of Archivefrontier. Instruments will have to be implemented which are not available currently. New freezing methods are being tested to optimise and speed up the

process. The community will have to be trained to work with such material. The proposed infrastructure aims to play a leading role on the worldwide level. Mouse centres where research and infrastructure coexist, and that are leaders with respect to excellence and national importance, will be selected to become part of this infrastructure. The European Mouse Mutant Archive, EMMA, the infrastructure network which includes the most experienced European research Institutions in the field, will coordinate this project.

4. The Concept case (maturity of proposal)

The main goal of functional genomics and mouse genetics in the 21st century will be the generation of mouse mutations for every gene in the mouse genome, creating a huge and vital resource of models for the study of human disease. Over the next decade, we can expect that tens of thousands of mouse disease models will become available, all of which will ultimately require archiving, dissemination and phenotyping. Current capacity to achieve this goal is limited. Indeed, existing facilities across Europe can offer capacity for the dissemination and analysis of around a few hundred disease models per year. It will thus be necessary to organise phenotyping, archiving, and distribution of mouse models on a well-concerted, large- scale, Pan-European level. Infrafrontier brings together well-experienced European laboratories with proven track records to implement and run large-scale infrastructures For the Phenomefrontier subproject two visibility studies have been undertaken. 1. Eumorphia performed the development of standardised and validated phenotyping assays in a wide variety of indications. 2. Eumodic, which is in the starting phase, will for the first time undertake large-scale phenotyping in a cross-laboratory effort. Both project show clearly the well-organised scientific community and provide a structure, which will be developed for Phenomefrontier.

Archivefrontier will be coordinated and run by the European Mouse Mutant Archive "EMMA". Archivefrontier is necessary to restructure the existing infrastructure. New members will be added and existing partners will have to undergo major upgrades to fulfil the upcoming demands of the scientific community. EMMA was able to show great success in archiving and distribution of mouse models over the last years. This experience will increase the chances of success.

Criteria have been developed to choose the essential and necessary partners for Infrafrontier. The selection process includes national scientific organisations, national bodies and independent scientific advisory boards.

The establishment of such an infrastructure will result in mutant mice becoming much cheaper, with an estimated decrease of the cost per strain by a factor of 5 to 10, while archived mice will not come with a series of restrictions, with a commercial supplier retaining the IP rights. NIH is planning such a bank of mutant mice and therefore Europe needs to keep pace and establish a similar infrastructure to be competitive.

The project plan for Archivefrontier is mature and can be started anytime. Phenomefrontier can be started in 2007.

5. Further information, including strategic importance to ERA

Infrafrontier is necessary to ensure the appropriate coverage of phenotyping and archiving infrastructure in the different areas of Europe. Infrafrontier is expected to give Europe a leading position in a worldwide competition on resources and knowledge for medically relevant mouse models. Europe will need such a infrastructure to make efficient use of emerging resources.

6. Identification of other socio-economic impacts

The launch of Infrafrontier is required to speed up the discovery of molecular mechanisms of diseases and health - this is an important step for the future of molecular medicine and the advancement of diagnosis and

therapy. Academia and industry will have to work together to develop new instruments and technologies for *in vivo* imaging using non-invasive methods. Infrafrontier will not only be responsible for this task within Europe it will take a global lead and will play an important part to ensure the appropriate advancement in science and the future of molecular medicine.

7. Participating organisations / support from Member states

The success of Infrafrontier will depend on the quality of its participants. Relevant parties involved with proven excellence in mouse technologies and the development and analysis of mouse models simulating human diseases are the Eumorphia/Eumodic- and EMMA-consortium (*e.g.* CNR, CNRS, MRC, Gulbenkian, Karolinska, HGF/GSF, EMBL-EBI, BSRC Fleming and others). The strongest players in Europe have committed themselves to implement and run Infrafrontier. This list is not exclusive and additional members will be selected through the procedures detailed below. It will be important to bring together all the significant players in Europe as Infrafrontier develops.

The evaluation process for inclusion of new members has been started. 17 member states of the EU have used EMMA and Eumorphia within the last year – besides USA, Australia, Japan and China. Involved EU member states committed themselves to co-fund the project through national grants or organisations.

Rules for taking on prospective new partners into the EMMA network

The EMMA archive and the workload for distributing mutant mouse strains are rapidly growing. Due to large scale mutagenesis projects such as EUCOMM the number of strains archived by EMMA is likely to double within the next three years. In order to share the increasing workload new members will be incorporated into the EMMA network and guidelines for this process were established. The selection process of prospective new members must be carefully designed to avoid the formation of to many satellites which would lead to a network structure where it is difficult to keep the high EMMA quality standards and which would be difficult to be managed effectively.

Rules for taking on prospective new members representing new countries

For prospective new members representing new countries EMMA retains the 'one node per country' policy. A responsible body of the new member country e.g. a national government, a ministry or institution will propose to EMMA which organisation might join EMMA. The EMMA board of directors and institutions expressing interest in becoming an EMMA member will initiate the process which new member country joins the EMMA network. Potential new members

- must be actively involved in mouse research with international impact

- must have existing archiving capacity

- must represent a country

- must not specialise on specific disease models with respect to the archiving activities

Rules for taking on prospective new members within current member countries

Currently the EMMA network follows a 'one node per country' policy as defined by its supervisory board. In exceptional cases EMMA will grant a special membership to institutions of EMMA network member states. The Sanger institute and ICS Strasburg were offered a special membership whilst these institutes are actively involved in large-scale mouse functional genomics project of international importance and scale. The special membership involves a 2-year test phase; members must join a contract and will be offered a seat in the EMMA Board of participating directors.

Funding of new members

Prospective new members normally won't be able to join existing EU contracts. Funding must be provided by either the joining institutes or national funding bodies. The operation of new partners is possible on a cost recovery basis. However, new members can be partners in new grant applications.

8. Budgetary information

Preparatory cost (total in M€)	Construction cost (total in M€)	Operation costs total in M€))	Decommissioning cost (total in M€)
50 M€ Benchmarking, international symposia, construction plans, first preparatory steps for constructions and major upgrades. Lawyer costs for consortia contracts.	**270M€** Phenomefrontier – 150 M€, Archivefrontier - 120 M€ Construction of new facilities and major upgrades of the existing facilities	**36 M€ per year** Phenomefrontier – 24 M€ per year , Archivefrontier - 12 M€ per year Assigning new phenotypes to new mouse models from different pipelines. Archiving new mouse models including attached data sets within an upgraded database.	**Not applicable**
(of which likely to be obtained by possible stakeholders) 50%	(of which likely to be obtained by possible stakeholders) 50%		(of which likely to be obtained by possible stakeholders) -

9. Timetable until operation

Give a short estimation about the timetable until operation

Preparatory phase	Construction phase	Construction and operation phase	Decommissioning
2006-2007	2007-2017	2007-2017	-

10. Contact

Prof. Steve Brown, <s.brown@har.mrc.ac.uk>

Prof. Martin Hrabé de Angelis, <hrabe@gsf.de>

http://www.eumorphia.org/ http://www.emma.rm.cnr.it/

1. Name and descriptive title

European Biobanking and Biomolecular Resources Infrastructure

2. Short description of new RI (or major upgrade) and main characteristics

A pan-European, broadly accessible, networked database and biological resource system of collections of well-documented, up-to-date clinical, biological, epidemiological and life-style data. It will include samples from patients and healthy persons, molecular genomic resources and bioinformatics tools to optimally exploit this resource for global biomedical research. The proposal includes also biological resources from non-human species.

This proposal aims to build a coordinated, large scale European infrastructure of biomedically relevant, quality-assessed sample collections for improved pharmaceutical and biomarker R&D, to enhance therapy and prevention of common and rare diseases, including cancer. Combining broad access and flexible data integration with securely protected access, using genome-wide approaches and broadband automation technology, it will ultimately provide standardised biospecimens, annotated with clinical, molecular and life style data, and offer a platform to expand further resource development. In this area of unique European strength, valuable and irreplaceable national collections typically suffer from underutilisation due to fragmentation. Major synergism, gain of statistical power and economy of scale will be achieved by interlinking, standardising and harmonising – sometimes even just cross-referencing - of a large variety of well-qualified, up-to date, existing and *de novo* national resources. Such a clinical biobanking network requires the support of parallel access to common, validated reference material, genomic and population-genetic data and molecular resources that are cost-intensive and laborious to generate. Cooperatively, clinicians, pathologists and molecular biologists can thus build an Europe-wide, but globally unmatched platform for translational medical research, to speed up development of personalised medication and prevention. Moreover, this system will strongly boost political and scientific momentum to harmonise ethical, legal and quality standards across Europe.

3. Science case (scientific justification, including new areas to be opened)

Following the rapid progress in genomics research of humans and their ancestors, biomedical and health research has expanded from the study of rare monogenic diseases to common, multifactorial diseases. The advances in innovative, high-throughput technologies are widely expected to enable a better dissection of these complex, causally heterogeneous diseases into more homogeneous subgroups. A sharper, biology-based definition of disease categories will enhance success in clinical trial design, the development of more effective treatment, reduce undesired side effects and improve prevention. However, most complex diseases are elusive as they do not root in single defects, but are caused by a large number of small, often additive effects from genetic predisposition, lifestyle and the environment. *Discovery*, i.e. separating the signal from the noise, will depend critically on the study of large collections of well-documented, up-to-date epidemiological, clinical and biological information and accompanying material from large numbers of patients and healthy persons, so-called biobanks. The biological materials collected in biobanks for biomedical research typically comprise DNA, tissues, blood or other body fluids. Biobanks are widely considered as a key resource in unraveling the association between disease subtypes and small, but systematic, variations in genotype, phenotype, and lifestyle.

The strength of a combined approach to interface, harmonise and where possible integrate the European biobanking resources, lies in a combination of four complementary biobank formats, each with its own

strength, to render their combination much more powerful than each resource type individually. This provides the best possibility to define and correlate healthy, pre-clinical and clinical profiles, and will strongly boost the integrated study of biological and genetic disease mechanisms, improve the delineation of clinical phenotypes and establish biomarker spectra for disease prognosis and therapy monitoring. These four biobanking formats existing in Europe are:

- *Longitudinal population-based cohorts*, followed prospectively, either initiated *de novo* or continued from ongoing endeavors, sometimes already for decades, these are valuable to assess the natural occurrence and progression of common diseases and to classify disease subcategories. Once genetic risk factor variants are identified, the population cohorts provide a setting to estimate their real quantitative and qualitative impact on health and disease in the population.

- *Clinical case/control populations*, having a much higher incidence of the relevant disease, are the optimal platform to validate discoveries of genetic and non-genetic factors, without having to wait for great lengths in time and spend large efforts on further longitudinal, prospective collection. The selected, increased contrast between patients and controls in these cohorts, often also followed up for many years or decades, can be used to recognise disease profiles against a background of naturally occurring variation. In addition, and in particular when enriched with state-of-the-art biospecimens and data, these populations are invaluable for finding biomarkers for early signs of disease, progression, mortality, and for response to treatment.

- *Population isolates* allow unique advantages for the identification of genetics risk profiles. They have the additional advantage of a more homogeneous genetic structure and environment. Thus the tracing of predisposing genetic factors, which can, in turn again, be quantitatively validated in longitudinal cohorts and disease populations is facilitated. Many collections of family resources in different European countries represent resources comparable to population isolates in the gene identification.

- *Twin registries* contain about equal numbers of monozygotic (MZ) and dizygotic (DZ) twins. This allows the parallel dissection of the effect of genetic variation in a homogeneous environment (DZ twins) and of environmental effects against an identical genetic background (MZ twins). This aids in establishing profiles in healthy and affected individuals of different ages, in assessing the individual variation in profiles, and in dissecting genetic, epigenetic and environmental influences at the biomarker level.

Activities envisaged:

Peer assessment and structure optimization. To optimise the resolution of the disease entities existing resources need to be peer-reviewed for the nature and the structure of the data collection, quality and linking possibilities. For optimal value retention, pragmatic adaptations to interface a decentralised informational structure and access must take priority over overly rigorous centralisation and integration.

Clinical phenotyping. Where necessary this process will highlight opportunities for additional phenotyping, *i.e.* collection of further clinical, environmental and lifestyle data. Based on experience in current programmes, about 50-70 per cent of the resources will be of sufficiently high value to justify enrichment, expansion, or the exploration of new parameters and angles. Ongoing and yet to be established *de novo* biobanks will be actively incorporated into the infrastructure. They have the advantage of *ab initio* formulation of scientific and ethical standards. The disadvantage of longer time-to-benefit can be remedied to a significant extent by interfacing them with improved and enriched retrospective biobanks.

Molecular phenotyping. The biobank resources will not only be focussed towards genes and their functions. Increasingly we have become aware of the intricate crosstalk between the different levels of living cells and organisms, including the protein and metabolite levels. Hence the biobanking resources need to facilitate research in genomics, proteomics and metabolomics. This will require further enrichment of the existing resources with additional, molecular phenotyping.

Genotyping. The number of detectable genetic variants in humans in publicly available databases has increased from several 10,000s only a few years ago to 10 million today. In addition, the technology to find these variants has made equal if not greater progress. After recent, large-scale, public/private efforts such

as the HapMap consortium, aided by high-throughput technologies, the determination of hundreds or thousands of genetic variants in thousands of individuals has now become feasible. Thus, the generation of comprehensive, whole-genome genetic profiles, as well as their association to phenotypic health and disease traits, has now become feasible, but only to parties who are prepared to make significant investments to stay at the forefront of translational research and prognostic possibilities in this field. The collection of these data is just as much an integral part of the infrastructure as, for instance the gene annotation data in genomic databases. It shapes the basis of investigator-driven research into the correlation of clinical, molecular and genetic variation, which requires massive, advanced data storage, handling and analysis resources.

Ethical review. The state of European sample collections as well as the national regulations as to their use is quite diverse. An integrated biobanking programme will require the joint efforts of clinical and legal experts and the research and patient communities, to achieve standards and guidelines which properly balance individual values such as protection of privacy and informed consent, with shared values of facilitated access and progress in health care development. The standards implemented will also be in accordance with international guidelines as for instance discussed within the OECD.

Biological resource establishment and vertical, cross-species integration. With the maturation of genome research, genetic analysis of organisms has become much more widespread (more than 1,000 genomes have already been sequenced), and the need for more specific research material is accruing. Since the advent of large scale genomic sequencing in the 90's it is more and more common for biomedical research to specialise not in a particular organism but in a particular biological problem. These often have direct relevance to human disease, and many basic studies today have a clinical component. Indeed, much of our information about human diseases comes from model organisms. Thus, vertical integration, combining resources from different organisms in a single structure, improves the chance to create added value compared with the classification of resources along more organismal lines. The underpinning biomolecular resources take a variety of formats, generically described as gene-specific and validated tools for every single gene of an organism to decipher gene function, protein function, protein-protein interaction, or protein-"gene" interaction. Such validated tools (full ORF clones, siRNAs, antibodies etc.) are expensive to generate, and the costs for research on a genome-wide scale is often prohibitive. In many countries, local and national resources are being generated, and the enablement, and where possible integration of their facilitated access is crucial to maximise the potential of biobank research.

The establishment of biobanking and genomic resource infrastructures have different scientific, ethical-legal and socio-political frameworks. It is envisaged that under this programme, applications do not need to cover all bases individually. Rather, optimally complementary and sufficiently mature proposals in both areas should be considered in parallel.

4. The Concept case (maturity of proposal)

This proposal integrates existing epidemiological, clinical and biological data on massive European study samples, to provide study sample infrastructure for genome-wide analyses (databases, sample handling logistics and platforms), as well as forming a standardised platform to ongoing and future biobanking. Large initiatives already exist on national and multinational level throughout Europe in the complementary fields of longitudinal, case-cohort, isolate and twin collections. Their coordination into a common system, establishing a standardised quality control, agreement on data exchange formats, data interfacing and where possible integration, and harmonization of annotation, will tremendously enhance spin-off in health care, well-being and productivity. This can be implemented stepwise, on an overall time scale of 2-10 years. The build-up is triphasic: harmonization of epidemiological, clinical, and life style information, definition, triage and interfacing/ integration of existing resources occurs in years 1-3. Further enrichment and supplementation occurs in years 2-7 and expansion and further *de novo* foundation (in part targeted to lacunes in the previous materials) in years 3-10. While in principle, integration of biomolecular and cellular resources may be achieved more rapidly, new resources will continually emerge, so here, too, a 2-7 year build-up is envisaged.

This integrated retrospective/prospective biobanking approach is more effective than the exclusive reliance on *de novo* established biobanks, as these, by themselves, will only bear fruit after 10-20 years. Moreover, a combined retrospective/prospective approach makes the most sensible use of the estimated 1-1.2 million extensively annotated samples already present in high-quality collections in the European health care system. A significant fraction of these of these can be used for combined epidemiological/ molecular pathway elucidation, drug discovery and prevention development in a relatively short time, (realistically 4-7 years including ramping-up). This field is one of the most robust and unassailable existing strengths of European biomedicine, it has been provided by the European health care system, and European tax payers could thus get properly rewarded for their investments.

5. Further information, including strategic importance to ERA

European research will profit enormously, when cutting edge epidemiological, clinical and research material in life sciences are harmonised, integrated and high-quality databases are produced at the European level, instead of being restricted to research projects and clinical environments in the countries where they were generated. Great strength and global competitiveness will be gained when this resource will be available without undue restrictions and precocious IP claims throughout the ERA. Using innovative IT approaches and peer-based quality assessment, high scientific and ethical standards can be applied centrally even to decentralised resources. Integration of thus validated materials and scientific data will foster insight into complex diseases and biological pathways. This will obviate redundant and fractionated, underpowered analyses and waste of valuable material. Researchers can concentrate on formulating more powerful questions, speeding up scientific progress and implementation, rather than on generating, or often even duplicating, research material. Open-ended searching allows the unexpected to emerge, revealing whole new horizons. The availability of sufficient well-characterised biospecimens from legitimate sources will allow European pre-clinical/clinical research to take a frontline position commensurate with the advanced quality of our health care systems. This will prevent discoveries and valuable downstream IP inventions from draining to non-European countries at the cost of European jobs and ethical standards.

6. Identification of other socio-economic impacts

Given the limited finances for fundamental and translational research, the scarcity of high quality tissue specimens, and the high cost of extensive clinical and environmental enrolment of patients and healthy control donors in state-of-the-art biobank collections, it is vital not to replicate work that has already been done. Instead, such efforts, once done, needs to be widely exploited, while at the same time safeguarding the consistency, quality, and sustainability of the resulting resources and/or data. This applies equally to ongoing and catch-up research, in old and new member states. This proposal will safeguard the long-term availability of valuable resources, irrespective of the funding of research projects, institutes, or positions by means of which they were generated. The pharmaceutical and biotechnological industries would greatly benefit from wider access to properly validated resources, available without undue restrictions, except for suitable, harmonised ethical safeguards. Shared access to unlocked clinical and biological resources between academia and biotechnological and pharmaceutical industries would not only accelerate progress in basic biological research, but more importantly, bridge the distance between public and private translational R&D. This will significantly reduce attrition rates of preclinical and clinical drug development. The outcome of this research will also provide a framework for better informed actions in health care and disease prevention, not only in Europe, but world-wide.

7. Participating organisations / support from Member states

The network should cover most existing infrastructures for various formats of biobanking and molecular biology and tissue based research. Without the aim of completeness or exclusivity, possible partners, many

of which currently funded and operational at a national level, might include:

1. Blood, sample and DNA banks, dedicated both to prospective, longitudinal, epidemiological and to case-control, disease-specific research, such as:

- The Estonian Biobank
- The Icelandic (Decode) biobank
- The UK Wellcome Trust Case-Control Consortium
- The UK Biobank
- Scandinavian Biobank Resources: Swedish, Norwegian, Danish and Finnish longitudinal, case-control and isolate collections
- The Danubian Biobank (Germany, Austria, Hungary)
- The Netherlands Biobanking Consortium
- KORA, Augsburg/Munich, Germany
- Inserm Biobanks, France
- The Genome Austria Tissue Bank (Bioresource-med, Medical University of Graz)
- Other biobanks of sufficient size and power, notably for population isolates, also in the new Member States
- Health-research oriented twin registries as collected in the GenomEUtwin Integrated Project

2. Molecular resource centers and technology networks, supplying facilitating environments for (temporarily) expensive technologies, cell culture facilities, and providing clone sets and resource libraries for functional studies, body fluids screening and molecular interaction mapping, *e.g.* siRNAs and shRNA libraries, collections of hybridoma lines, antibodies and/or protein arrays, as well as resources for model organisms of biomedical relevance, like zebrafish, *C. elegans*, fruitfly etc. Examples of resource centers, technology providers and networks in Europe are:

- KTH, Stockholm, Sweden
- Centre National de Génotypage, Evry, France
- Leiden Genome Technology Center, Leiden NL
- The Finnish Genome Center, Helsinki
- DSMZ, Braunschweig, Germany
- RZPD, Berlin/Heidelberg, Germany
- European Collection of Cell Cultures ECACC, UK
- Eurogentest EU FP6 network, www.eurogentest.org
- MolTools (www.moltools.org) and ProteomeBinders FP6 networks,

- Human Proteome Atlas, www.proteinatlas.org

- French national institute for agronomic research (INRA)

- European Biological Recource Centre Network (EBRCN), Belgium

3. Finally there is a need to involve bioinformatic centers to ensure that databases of samples in the repositories are dynamically linked to existing bioinformatics databases, and links to literature etc. Examples:

- EBI, Hinxton, UK

- Karolinska Institute (the database core of GenomEUtwin), Stockholm, Sweden

- NBIC, Nijmegen/Amsterdam, NL

- Weizmann Institute, Rehovot, Israel

- or new ones founded especially for the purpose

Such a complex network need not be implemented all at once, hence the multiphasic growth trajectory proposed, to be achieved step by step around clearly identifiable nodes of high quality and critical mass.

8. Budgetary information

Preparatory cost (total in M€):	Construction cost (total in M€):	Operation cost (total in M€):	Decommissioning cost (total in M€):
70 million € Pilot phase, SWOT analysis, peer review of biobanks and biomolecular resources. Harmonisation of ethical guidelines. Interfacing of existing databases. Setting up of common databases. Decisions on and pilot implementation of standardization, harmonisation and preparation of resources and data.	**100 million €** Setting up networking infrastructure. Set up of appropriate storage systems. Set up of common hardware and major upgrade of existing systems. Further enrichment and extension of clinical databases with phenotyping and genotyping data. Identification of white spots, opportunities	**100 million €** Consolidation and maintenance of common database infrastructure. Extension of resources and data. Further harmonization and standardization of resources.	**Not applicable**
(of which likely to be obtained by possible stakeholders) **20 million €** National bodies, charities, industry	(of which likely to be obtained by possible stakeholders) **70 million €**	(of which likely to be obtained by possible stakeholders) **50-100 million €**	(of which likely to be obtained by possible stakeholders) *****

9. Timetable until operation

Give a short estimation about the timetable until operation			
Preparatory phase Years 1-3.	Construction phase Years 2-7	Operation Years 3-10	Decommissioning Years >10

10. Contact

Prof. Leena Peltonen-Palotie, Director of GenomeEUtwin
Department of Medical Genetics, University of Helsinki

Email: leena.peltonen@ktl.fi
tel: +358-9-4744-8393
fax: +358-9-4744-8480

www.biobanks.eu

1. Name and descriptive title

Network of Distributed Infrastructures for Clinical Trials and GMP Biotherapy Facilities in Europe

2. Short description of new RI (or major upgrade) and main characteristics

The capacity of the European Union to perform highly competitive clinical research, and to promote innovative pharmaceutical and biotechnology development requires an integrated, EU-wide clinical research infrastructure, bridging the fragmentation of Europe and allowing high-quality, multinational clinical trials. This infrastructure will be based on the upgrade and integration of existing infrastructures, through :

- The **interconnection of national networks of clinical research centres and clinical trial units**, through a multinational coordination team, and through European correspondents embedded in the national network of each member state. Shared procedures will enable industry or academic clinical research projects to be carried-out in any medical field, with high quality GCP standards across the whole EU, thus enlarging and accelerating patients' recruitment.
- The upgrade or creation of new facilities supporting the production and the evaluation of innovative biotherapy agents.
- The availability of professional **data centres** allowing high quality data management across the EU
- And its connection with disease-oriented **patients** associations and registries, and disease-oriented **investigators** networks in order to foster patients' enrolment.

The multinational clinical trial network will give a substantial contribution to surmount the growing bottleneck of transfer of innovative medicines developed by translational research to improved medical care.

3. Science case (scientific justification, including new areas to be opened)

Development of diagnostic and therapeutic innovation, and delivering improved health care to EU citizens requires clinical research during the whole process extending from understanding the mechanism of disease, genetic studies or identification of biomarkers, to the clinical development and evaluation and to post-marketing strategy trials. The recent development of therapeutic innovation is mainly based on biopharmaceuticals and on personalised treatments, on pharmacogenetics and toxicogenetics, on the use of biomarkers, and **requires access to large populations of patients**, enabling clinical trials adopted to these new therapeutic strategies with a need to focus on specific patient subpopulations. In addition, the quality of investigation, the quality of clinical and biological data, and the rate of enrolment of patients in these innovative clinical trials, hence the quality of the infrastructure, will be the main factors of competitiveness for European clinical research. European academic research, as well as the pharmaceutical and biotechnology R&D need an efficient, integrated and professionalised organisation of clinical research, based on competences centres able to provide efficient support through a consistent set of services for clinical trials. **Infrastructures supporting patients' investigation, data management, quality assurance, monitoring, ethics and regulatory affairs are required for quality and credibility of data**. An integrated, EU-wide infrastructure, will allow the conduct of multinational studies in Europe, taking advantage of the EU population and competences, unlocking latent expertise and patients currently scattered across the EU

member states.

It will also participate in the long-term **structuring of disease-oriented networks** (including NoE and IP), helping them to connect and to collaborate across national borders. In turn, disease-oriented networks will provide the integrated infrastructure with **multinational projects** and with **multinational patient registries and cohorts**.

Such an integrated infrastructure will benefit the scientific community for the next 10-20 years, enabling it to further understand the mechanism of diseases, to identify new targets of innovative treatments and new biomarkers, to identify responder populations, to develop innovative diagnostic and therapeutic tools. This integrated infrastructure will be of particular relevance in **rare diseases**, however the **personalised approach** regarding efficacy and safety of treatments requires extended networking as well.

These concerns are identified as bottlenecks to be addressed in the **Innovative Medicines Initiative (IMI) strategic research agenda**, and its implementation will require an infrastructure enabling high quality clinical trials to be performed across the European Union with harmonised tools and practice. If implemented, such an infrastructure would give Europe a scientific advantage by improving and accelerating transfer from basic research via clinical research into better medical care.

4. The Concept case (maturity of proposal)

A model organisation for such an EU- wide integration of clinical research is illustrated by the European Clinical Research Infrastructures Network (ECRIN). ECRIN is based on the connection of national networks of clinical research infrastructures. Clinical research centres (CRC) and clinical trial units (CTU) are **infrastructures** acting as **competence centres** based on the **know-how** and providing access to clinical research projects originating from the scientific community : academic scientists, investigators, or industry sponsors. Professional staff trained according to Good Clinical Practice (GCP), hospital beds, equipment devoted to clinical research, and standard operating procedures (SOP) ensure a high-quality level in the design and the conduct of clinical studies in any medical field.

National networks of CRC and CTU were recently created in some EU-member states. However the need for harmonisation and ability to conduct multicentre projects is even greater at the European level, and therefore there is a need for an integrated infrastructures network designed to bridge the fragmented organisation and to improve the quality and efficiency of clinical research in Europe.

The ECRIN[1] programme started with a first FP6 funding in 2004, allowing identification of bottlenecks to multinational clinical studies across the borders of the EU (see reports on www.ecrin.org).

A second FP6 funding (2006-2008) helps prepare the network to become a EU-wide infrastructure, through 6 working groups in charge of defining guidelines and procedures for multinational studies (on ethics, regulation, adverse event reporting, monitoring, data management, and quality assurance). In addition, the current programme will help enrol and train a coordination team and European correspondents in each participating country, and competence accumulated during this programme will be used to run the infrastructure at the next step.

Upgrade of the project (2008) to provide a full functioning network of distributed infrastructures for Clinical Trials in the EU will consist of :

1- strengthening the **coordination team and the European correspondent teams** to run the

[1] Demotes-Mainard J, Ohmann C : European Clinical Research Infrastructures Network : promoting harmonisation and quality in European clinical research. Lancet 2005; 365, 107-108.

infrastructure, namely to provide a co-ordinated support to clinical studies, including :

- support in the interaction with ethics committees
- support in the interaction with competent authorities and in regulatory affairs
- support in adverse event reporting
- support in drug dispensing
- support in the circulation of biological samples
- support in study monitoring
- data management

2 - the set-up of **data management centres** allowing remote data entry, compliant with the EMEA and FDA requirements, with the corresponding data centre staff. In a first step, equipment of 5 to 10 data centres across Europe, using compatible standards for data management will help the EU to cover the needs from the scientific community (academia and industry) and to reach high-quality standards.

3 – coupling this network with a network of 3-4 centers able to produce clinical grade biotherapy agents (gene, cell and tissue therapy). Infrastructures are necessary for the production of new potential therapeutic agents derived from biotechnology, in particular infrastructures dedicated to the production of clinical grade vectors for gene, tissue and cell therapy. The development of production of adapted vectors and cells needs the construction of laboratories compliant with the current Good Manufacturing Practice (cGMP) and in agreement with measures of prevention against the dissemination imposed by the regulation related to the Genetically Modified Organisms, Through this coupling, the project is to construct centres encompassing all the structures involved in the preparation of clinical grade vectors and regenerative medicine products in the translation to clinical trials, with the goal of coordinating the participation of clinical teams, researchers and laboratories.

4 - **extension of the network** to additional EU member states. ECRIN currently includes six European states, and the programme plans an extension to existing national networks in other member states, and stimulates the set-up of national networks for further connection to the European infrastructure.

5. Further information, including strategic importance to ERA

European perspective and added value for member states

Health and legislative systems in Europe fragment clinical research and dampen its competitiveness, reducing the capacity to enrol patients in clinical studies, increasing the costs of clinical research, and hampering scientific productivity.

For the **European Union**, this infrastructure will promote bottom-up harmonisation, spread quality standards, and provide the EU with a network of harmonised competence centres, increasing the competitiveness of Europe as a knowledge-based economy as expected in the Lisbon agenda.

For **public sponsors**, this infrastructure will help address scientific challenges (eg, in studies on the mechanism of disease, genotype-phenotype studies), public-health challenges (eg, trials beyond the scope of industry investment, including orphan drugs, rare diseases, strategy, surgery trials), or research and development challenges (eg, biotechnology, in which public-private partnership is common).

For **industry sponsors**, harmonisation of practice within Europe and improved quality will facilitate the conduct of industry-driven drug development, and will provide support to SMEs (eg, biotechnology and medical-device companies) willing to act as sponsor in the development of innovative diagnostic or therapeutic tools.

In addition, this project will lead to **long-term structuring effects**, affecting the organisation of clinical research, at national and European levels, promoting shared and harmonised policies, and affecting the **scientific competitiveness** of Europe in biomedical research.

This programme will also **directly impact at the national level**, spreading the best practice across the EU and providing them with high quality centres and networks. In **countries connected** to the network, this programme will strengthen the networks and promote centralised tools and facilities, thus avoiding duplication of efforts. ECRIN already has an impact in **countries not yet connected**, as it stimulates the structuring of networks, and will spread harmonised quality and unlock latent scientific potential, particularly in new Member States.

Finally this infrastructure will impact on the FP7 **Innovative Medicines Initiative** (IMI), facilitating clinical trials for both industry and academic projects, increasing the efficacy and competitiveness of drug development by the European industry.

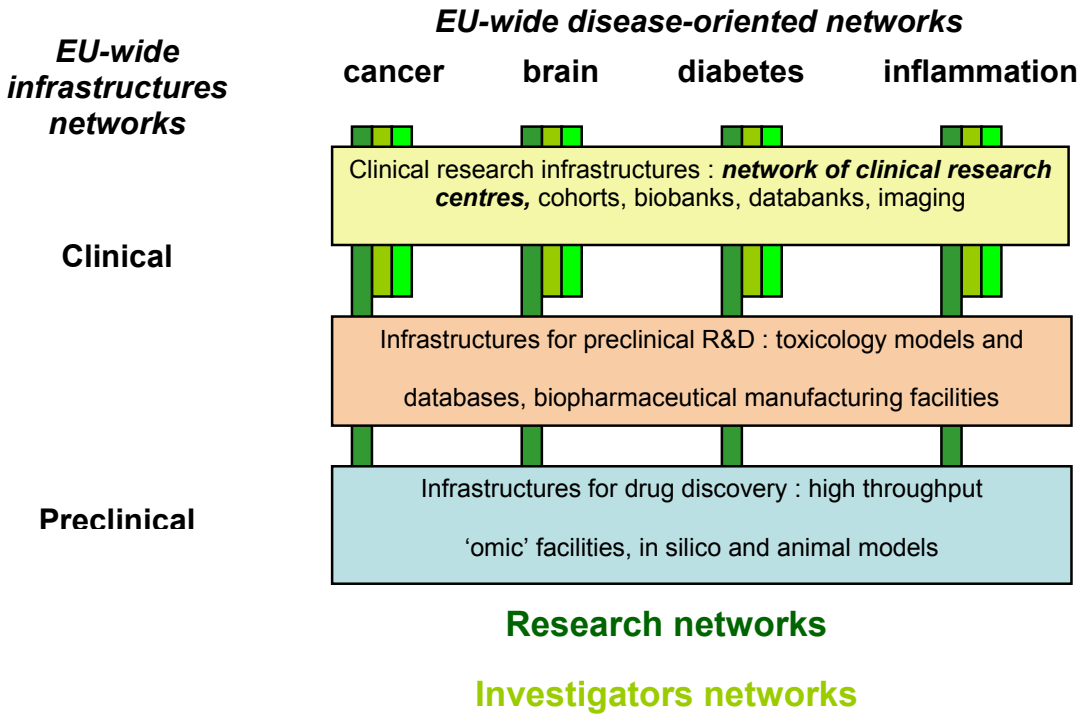


Fig.1. Model for Europe-wide infrastructures and disease-oriented networks

From : report of the Barcelona workshop 'How to establish a European technology platform for innovative medicines', April 20-21, 2005

6. Identification of other socio-economic impacts

As previously stated, this programme will impact on the **competitiveness of both academic and industry biomedical research in the EU**, hence the capacity of Europe to **develop new treatments and to improve citizens' health**. The competitiveness of European clinical research will be based on the quality of its infrastructure, therefore on the quality of clinical and biological data, and on its capacity to enrol patients at a higher rate : **the duration, not the cost, of clinical trials is the key competitive factor**. Reducing by a few months in the development of a new treatment

saves hundreds of millions Euros, and this far exceeds the difference between the cost of clinical trials between Europe and Asia. Moreover, ECRIN will develop the capacity to support both academic and industry sponsors in transnational studies, and this will be critical to the development of **European biotechnology and medical device SMEs** who lack the capacity to perform the increasingly complex sponsors tasks for clinical trials in Europe, thus increasing their capacity to grow and to access the market.

In addition, it will foster the **participation of patients** and patients associations, and their education as well as the awareness of the general population on clinical trials through a **yearly communication event** (the May 20th 'International Clinical Trials Day'). Finally, European correspondents and the coordination team trained during programme will **spread know-how** on the conduct of clinical research across the EU member states.

7. Participating organisations / support from Member states

In this distributed infrastructures network, the EU member states provide support to their national networks, and the EU to the coordination, the European correspondents, and the data management facilities. As this infrastructure mainly consists of a network of competence centres based on the know-how, operation costs are critical for its implementation.
Six national networks are already involved (Denmark, France, Germany, Italy, Spain, Sweden), and the current preparatory project plans an extension of the network to the other EU members states (currently negotiations are ongoing with Hungary and with the UK). The objective is to cover all the EU member states.

8. Budgetary information

Preparatory cost (total in M€) **1M€**	Construction cost (total in M€) **5M€** for 10 data centres **30 M€** for GMP biotherapy units	Operation cost (total in M€) **29M€** Coordination : 4M€ over 6 years; European Correspondents 15M€ over 6 years; Data centres : 10M€ over 6 years for 10 centres	Decommissioning cost (total in M€) NA
(of which likely to be obtained by possible stakeholders) M€	(of which likely to be obtained by possible stakeholders) M€	(of which likely to be obtained by possible stakeholders) M€	(of which likely to be obtained by possible stakeholders) NA

9. Timetable until operation

Preparatory phase
CRC network (already prepared) and data centres : Year 1

Preparatory phase	**Construction phase**	**Operation**	**Decommissioning**
CRC network (already prepared) and data centres : Year 1	CRC network : year 1 Data centres : year 1	CRC network : pilot projects on year 1 Data centres : year 2	NA

10. Contact
Jacques Demotes-Mainard, MD-PhD Co-ordinator, ECRIN Programme European Clinical Research Infrastructures Network http://www.ecrin.org/ CIC INSERM / CHU de Bordeaux CHU Haut-Lévèque F-33604 PESSAC, France tel: (+33) 55765 6170 mobile:(+33) 62213 6791 fax: (+33) 55765 6168 demotes@bordeaux.inserm.fr

1. Name and descriptive title

EATRIS - European Advanced Translational Research Infrastructure in Medicine

2. Short description of new RI (or major upgrade) and main characteristics

Despite tremendous progress in the life sciences and increasing investments of the pharmaceutical industry and biotechnology into research and development, we are observing a widening gap between discovery and translation into medical products and applications. New results from basic science are not translated into clinical practice and patient care – or the translation is slow and incomplete. Translational research in medicine is the link between basic or fundamental science in biology and medicine and implementation of results from these research areas into clinical diagnosis and treatment in hospitals. Since an elaborate process of target assessment, identification and optimization of model compounds, repeated testing under various conditions, GMP (good manufacturing practice) production and regulatory approval have to be encompassed in translational biomedicine, this field constitutes a tremendous challenge. Finally, new products have to be evaluated in clinical trials

There is a striking gap between basic science and clinical medicine that is much more pronounced in Europe than in the USA and that has tended to widen in most European countries due to increasing clinical demands and reduction in hospital budgets. In the end this will have serious consequences for health care, biomedical research and biomedical industries in Europe. Thus the implementation of a large infrastructure for translational research that links and engages both clinical and basic scientists as well as strong industrial partners is of key importance.

As a first step to achieve international leadership, we propose an EATRIS consortium built on an initial core of advanced European research centers with a strong translational mission in diseases that are of major importance to the European population. They will have the primary goal to significantly promote the transfer of research findings into clinical practice.

The centers will closely interact and will serve as a nucleus for the European Advanced Translational Research Infrastructure. During later stages, additional dedicated centers are expected to join. This strategy is needed to secure for the European Union an international top position in the most important field of translational medical research.

It will also considerably strengthen the economic potential of health care markets in Europe, with a strong emphasis on "tech trans" from research to industry.

3. Science case (scientific justification, including new areas to be opened)

The life sciences are making dramatic progress in unraveling the causes and basic mechanisms of major human disorders. Translation of research findings into innovative strategies for the diagnosis, treatment and prevention of common diseases for which efficient treatments are frequently lacking, represents one of the biggest challenges for European medical research, for the health care economy and for the European biomedical industry. Major progress in this

complex and demanding field requires a dedicated translational infrastructure with interdisciplinary expertise. We here propose a 3-step model with the initial development of 5-10 linked advanced European research centers with a strong translational mission as core for EATRIS.

These core centers will coordinate the inclusion of additional centers to achieve rapid development of a pan European network as foreseen in the fully implemented EATRIS.

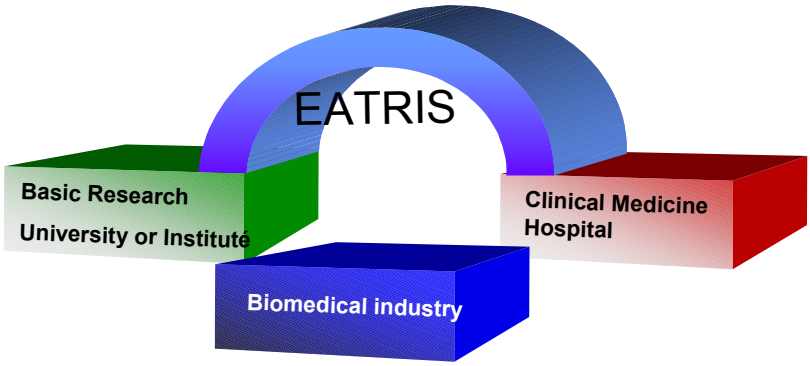
EATRIS will focus on the following major areas, chosen because they cover some of the largest and most important disease areas in Europe:

- Cancer
- Diseases of the cardiovascular system
- Brain disorders & advanced imaging
- Metabolic syndrome
- Infectious disorders & High security facilities

A strong collaboration with the "Network of distributed infrastructures for clinical trials in Europe" will facilitate the transfer of innovative interventions into improved medical care and health strategies. Interactions with centers of excellence in basic research, with disease-oriented research networks and with partners from the medical and pharmaceutical industries will be mandatory. A consortium with linked core centers will advance translational research to a substantially greater extent than centers funded to do their own research. The consortium centers can share expertise, common challenges, technology platforms, research agendas, joint training programs etc.

Research results from leading European laboratories can thus be translated into clinical practice to obtain better patient care based on a systematic transfer of research findings from the bench to the bedside. An important task for EATRIS includes training of "the translators in medicine of tomorrow". Basic scientists in biology and medicine are not regularly exposed to clinical researchers in hospitals, and vice versa. EATRIS will train both sides to communicate, and do research together. At present new and very innovative ideas and discoveries in the field of medicine and biology often arise at the borders between disciplines.

EATRIS The European Advanced Translational Research Infrastructure in medicine

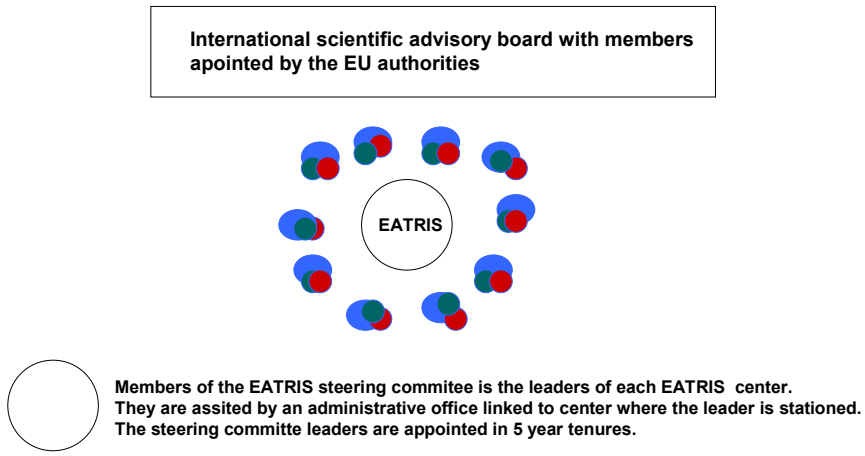


4. The Concept case (maturity of proposal)

Translation of laboratory findings into diagnostic, therapeutic and preventive clinical applications poses a major challenge for modern biomedical sciences. It requires considerable know-how and infrastructure for preclinical development in areas such as identification of target molecules, assay development, screening of molecular and chemical libraries, development of gene based therapies, medicinal and computational chemistry, antibody production, in vitro and in vivo validation, toxicological analysis and production of therapeutic agents under GMP conditions as well as development and implementation of novel biomarkers and diagnostic procedures. Such a daunting task can only be mastered in a dedicated translational R&D infrastructure.

EATRIS will establish a pan European facility for the critical field of translational research which initially incorporates a limited number of centers as a distributed infrastructure with Pan European open access. The core centers will contribute complementary expertise and will systematically interact with each other as well as with additional European and international researchers and clinicians. Validation of innovative strategies and their translation into improved medical care and public health will be achieved through a close link to the Network of Distributed Infrastructures for Clinical Trials and GMP Biotherapy facilities in Europe, access to patient cohorts via eg. EORTC, pathology, molecular medicine, advanced imaging, the European Biobanking and Biomolecular Resources Infrastructure, sophisticated data management via the Bioinformatics Infrastructure for Europe as well as links to programs for early diagnosis and prevention of major human disorders. Each of the EATRIS sites will establish alliances with strong partners in the pharmaceutical and biomedical engineering fields.

Organisation EATRIS



EATRIS will be coordinated by a steering committee of experts and will be supervised by an international scientific advisory board to be appointed by the participating EU member states, and with members from the European healthcare industry, European patient groups and from the EU.

The implementation of a strong European translational research consortium should proceed in several steps.

1. In step 1, five to ten centers will form the consortium and serve as models for translational research. Criteria for selection of centers are commitment and scientific excellence for translation in major disease areas, with strong elements in basic, translational and clinical science.
2. In step 2, EATRIS will be expanded and include additional strong institutions and the model centers will take mentoring responsibility for collaborating centers in the new member states, based on geographic areas.
3. In step 3, the EATRIS centers will establish a well functioning pan European translational research program, and the common strategy for translational research activities will be developed and applied. Individual centers will take responsibility for selected key technologies which they share with their partners. The strategy will be to implement translational research infrastructures in university medical centers of all countries within the EU in the final step of this proposal.

Stage 2 and 3 can be implemented in parallel. For entering new centers the inclusion criteria should be: Center with an already strong interface between basic, translational and clinical research, with an innovative profile for new diagnostic procedures and therapies in diseases with strategic importance for Europe, and commitment to EATRIS.

5. Further information, including strategic importance to ERA

EATRIS will establish 5 – 10 model centers for translational research with the highest level of excellence. These sites have the critical task to link basic science to translational and clinical research. Europe will again be competitive in this very important field, and will in the future be

able to take an international lead both in translational biomedical research and in the development, evaluation and application of novel medical applications.

The advanced translational research centers within the EATRIS research infrastructure will serve as a nucleus for European translational research. They constitute model centers, which develop joint programs for translation, clinical validation, data management, quality assurance, monitoring/auditing and training, education and exchange. In step 2, institutions from other countries including new member states will enter into a partnership with the model centers. The centers will actively participate and interact with major European research initiatives, including FP7-programs for translational research, imaging centers, animal models and the European Biobanking and Biomolecular Resources Infrastructure. With excellence as the main criterion, participating individual scientists may also apply for support through the ERC.

Based on the EATRIS infrastructure, European biomedical research and health care industry will cooperate closely with positive synergistic effects for both sides. European biomedical industry will thus achieve international top positions in key future markets. The potential benefits for the European population, for European patients and for the European economy are enormous.

6. Identification of other socio-economic impacts

The health care industry has developed into a global enterprise and will be one of the fastest growing markets worldwide. Close cooperation between academic institutions and the biomedical industry will be a key to international leadership. Europe has an excellent research base, a strong clinical tradition and internationally renowned industrial venues, but has not yet capitalised sufficiently on the translation of these resources into economic value or benefit for the European societies.

EATRIS, The European Advanced Translational Research Infrastructure in Medicine constitutes a strategic investment built on a strong cooperation between research centers, clinical centers and industry towards the goal to systematically exploit the dramatic progress made in European biomedical research and molecular medicine.

Translational research is a newly emerging field for which training and education schedules must be established. An additional task of the EATRIS infrastructure centers will therefore include the development of training and mobility programs in translational and clinical research for scientists, experts and staff from different countries and different contributing disciplines. The proposed consortium of translational research centers will grow into a powerful European research force. Close interactions with partners from the pharmaceutical and biomedical engineering industries will play an important role. The socio-economic impact for Europe will be very high – both due to rapid progress in novel biomedical applications for major diseases, but also due to the faster growth of R&D in the new member-states, facilitated by their EATRIS membership.

7. Participating organisations / support from Member states

Centers of excellence in translational biomedical research are currently established in a number of member states. They cover some of the major disease fields such as cardiovascular diseases, cancer, metabolic syndrome, brain disorders, infections and include cutting edge technologies. EATRIS will require funding to strengthen and to complement the appropriate research infrastructure and to gain maximum benefit from already successful translational research.

In order to win international leadership, a first step is proposed with 5-10 advanced translational research centers throughout Europe as a nucleus for the EATRIS research infrastructure. A joint effort by the European Union, national authorities and industrial partners is mandatory to achieve

this major goal. Participating centers should build upon already existing sites with excellence in translational research.

The centers listed below are indicative of centers that currently meet the criteria of excellence in translational research in major disease areas, with strong elements in basic, translational and clinical science, but the list is not exclusive. Centers will be selected for EATRIS on the basis of commitment and scientific excellence in translation. Additional members for step 2 and 3 will be invited in an open and transparent pan European process, and selected on the basis of commitment and scientific excellence.

Potential Centers, Examples:

- Cardio-vascular diseases. (eg. Imperial College London).
- Advanced imaging & CNS disorders (eg. Neurospin, CEA, Paris)
- Metabolic syndrome & diabetes (eg. Karolinska Institutet, Stockholm)
- Oncology (eg. German Cancer Research Center, DKFZ, Heidelberg)
- Advanced imaging & Cancer (eg. Free University, Amsterdam)
- Infectious diseases (eg. GBF National Center of Biotechnology, Braunschweig)

In collaboration with: EMBL, EORTC, Network of distributed infrastructures for Clinical Trials and GMP Biotherapy Facilities in Europe, European Biobanking and biomolecular resources infrastructure, The Innovative Medicines Initiative, local national public and private foundations, Siemens Medical Solutions, Philips Medical, The European pharmaceutical industry. Significant contributions from partners in the pharmaceutical and biomedical industries as well as SMEs are expected. For EATRIS centers in the new member states: The Reuter Foundation, The George Soros Foundation are relevant.

The budgetary information below is based on a core of 5 model centers.

8. Budgetary information

Preparatory cost (total in M€)	Construction cost (total in M€)	Operation cost (total)	Recommissioning cost (total in M€)
5 M€	250 M€(+ 555 for phase 2 and 3.)	300 M€	Not applicable
(of which likely to be obtained by possible stakeholders)	(of which likely to be obtained by possible stakeholders)	(of which likely to be obtained by possible stakeholders)	(of which likely to be obtained by possible stakeholders)
2,5 M€	200 M€+ 400 ME (phase 2 and 3)	200 M€	0

9. Timetable until operation

Centers will be constructed and fully operational within a period of 3 - 5 years: individual dates will depend on local conditions. Construction costs will be for buildings, labs, animal facilities, laboratory infrastructure and equipment.

Preparatory phase	Construction phase	Operation	Decommissioning
2007	2008-2010	Starting 2010-2012	

10. Contact

Prof. Rudi Balling, PhD

GBF National Center of Biotechnology, Braunschweig

D-38124 Braunschweig

balling@gbf.de

Denis LE BIHAN,
NeuroSpin, Paris
Tel : + 33 1 69 86 78 26
Fax : + 33 1 69 86 77 86
lebihan@shfj.cea.fr

http://www.eatris.eu

1. Name and descriptive title

LIFE-WATCH - Science and Technology Infrastructure for Biodiversity Data and Observatories

2. Short description of new RI (or major upgrade) and main characteristics

LIFE–WATCH will put in place the essential infrastructure and information systems necessary to collate both existing and new data on biodiversity and distribute this information with analytical and modelling capabilities to the scientific community and to other users in the public, commerce, and policy sectors. The challenge is to bring together the partly already existing separate components [species-level and ecosystem-level data from observations and from collections; data integration facilities; on-line analytical and modelling tools] and to add scientific value for the next generation infrastructure, operating as an observatory of our environment. It is not a matter of just merging the components, but to organise and manage these in a setting that allows for advanced data mining and knowledge development.

The components are categorised as follows:

(1) Infrastructure networks for data generation and data processing

(2) Facilities for data integration and interoperability [and scientific domain interaction]

(3) Virtual laboratories to allow for utilizing a range of analytical and modelling tools

(4) Service Centre to provide special services for European and national policies, and to provide research opportunities for young scientists.

LIFE–WATCH is an open access infrastructure. The user groups that directly will find their way to the LIFE–WATCH infrastructure come from the scientific community. The LIFE–WATCH Service Centre will use e-Learning techniques to further the application of data and services. The LIFE–WATCH management will specifically promote the use by young researchers, since this group is expected to develop innovative ways for performing research at the infrastructure's facilities.

Access to the digital services will be in different ways.

(1) Information retrieval, both directly by individual researchers, or by machine-machine interactions allowing for value added data combinations for specific uses.

(2) Experimenting by combining data sets with analytical or modelling tools facilitated by Grid enabled work flows.

(3) Requests for targeted data and/or analytical/modelling tools, which are not part of regular array of services. This may imply joint research projects to generate such data or to develop the required tools.

3. Science case (scientific justification, including new areas to be opened)

Biodiversity is the variety of life on earth, encompassing plant, animal and microbial species, the genes they contain and the habitats in which they live. Earth is a living planet and the role of biodiversity in maintaining the earth system is now increasingly understood and recognised. What is needed is a much more integrated approach to understand and predict biodiversity dynamics and to support scientifically ecosystem and nature conservation management policies for all regions in Europe, to provide such knowledge and expertise for the developing and mega-biodiverse countries. This is essential to allow for sustainable exploitation of the natural resources, and to continue to benefit from the goods and services provided by these resources.

Research areas that will benefit from the LIFE-WATCH infrastructure, and thus provide a challenge for the infrastructure to meet the related demands from the scientific community are (i) Discovery of biodiversity; (ii) Biodiversity patterns; mapping hot spots; (iii) Biodiversity processes; monitoring changes; (iv) Linking to remote earth observation data; (v) Systems biology, (vi) Nature conservation and management; (vii) Data challenges for the LIFE-WATCH infrastructure; (viii) Biodiversity e-Science.

4. The concept case (maturity of proposal)

Although data generation and data management facilities presently are often scattered and exist in different scientific communities, the technical plan for the new infrastructure is to apply an integrated approach from the very onset. This holds for the following categories of the infrastructure's specifications.

- Governance and management
- Infrastructure networks and instrumentation for data generation and data processing
- Facilities for data integration and interoperability (and scientific domain interaction)
- Virtual laboratories to allow for utilizing a range of analytical and modelling tools
- Service centre to provide special services for European and national policies, but also to provide research opportunities for young scientists.

The components of the LIFE-WATCH infrastructure have been designed, developed and tested in various national European and international projects. Although the integration of these components in the proposed infrastructure is a new challenge, the preparations so far indicate that the plans have a sufficient level of maturity.

Governance and management

Many stakeholder communities are directly involved in data acquisition, delivery and interpretation in the framework of the integrating LIFE-WATCH infrastructure. Their involvement and responsibility is crucial for reliable services, but can be in conflict with the requirement to establish a clear governance and management structure. This not unusual for large-scale infrastructures, but especially a reality for distributed and virtual facilities such as LIFE-WATCH. It is planned to organise the governance structure with the following bodies.

- The LIFE-WATCH board, with representatives of each financially contributing country. This board appoints the management and oversees the operations of the infrastructure.

- The LIFE-WATCH council, with representatives of the major scientific networks concerned
- The providers and users platform, with representatives of the interested European countries.

Infrastructure networks and instrumentation for data generation and data processing

Marine Observatories

A network of marine biodiversity observatories in Europe is be built based on properly networked existing sites. These sites (http://www.pml.ac.uk/biomare/site.htm) are either field sites supported by research institutes, the EU-BIOMARE network covering Europe's shores from Svalbard to the Canary Islands and the Azores in the Atlantic and from the Spain to Turkey in the Mediterranean (Feral et al., 2002), or they can be monitoring stations operated by national governments. Continued data collection and assimilation to maintain and update these long-term data series is essential. In the Network of Excellence MarBEF, the BIOMARE network is now being extended to include deep sea sites, both pelagic (CPR) and benthic.

Besides supporting scientific research on long-term and large-scale patterns and changes in biodiversity, the BIOMARE network intends to increase observational efforts by focusing on a limited number of biological, chemical and physical variables that should be measured using standardised methodology over a large area and over a long time period. These include the use of underwater measuring equipment on buoys or bottom stations and on-line communication of data through satellites, When protocols can be agreed on the European (and international) level, this will greatly increase our observational capacity without much additional financial input. These efforts will also be linked to the global Census of Marine Life and its Ocean Biogeography Information System OBIS.

Besides the BIOMARE network, which has been designed for biodiversity research, an already partly operational network of sea-floor observatories (submitted EU project) also include biological parameters. Seafloor observatories may provide continuous, long-term, multidisciplinary and time referenced monitoring from coastal areas to deep sea, overcome limitations of traditional ship-based expeditions for data and samples gathering, allow to study multiple, interrelated processes over time scales ranging from seconds to decades, allow near real-time or real-time communication of scientific data and advance research in the ocean (and earth) sciences addressing social important issues.

The potential of airborne and satellite remote sensing for marine biodiversity observation has been made explicit in another EU project HYMOM. New technologies are constantly being developed, for instance the use of underwater listening curtains to track the movement of tagged fish, bird, turtle and mammal species, the use of new sonar technology allowing fish populations to be traced tens of kilometres around sound sources, the use of new visualisation technology for the oceans and others. Such developments will result in new partnerships for EU-LIFE WATCH.

Terrestrial Observatories

LIFE-WATCH will establish a network of Instrumented long-term field (LTER) sites collecting data from harmonised observational programmes and experiments combined with distributed data centres, linked to synthesis and interpretation centres for the generation of high level information products for policy applications. Such networks have been prepared in various EU projects and are now being consolidated in the Network of Excellence ALTER-Net.

A European Network of in situ long-term ecosystem monitoring sites will identify and quantify the causal relationship between the drivers of environmental change and their impacts on biodiversity and ecosystems and the services they provide to society. Data from such sites will be used in conjunction with EO data, to provide the assessment and forecasting capability needed to support future environmental policy, planning and resource management decisions on biodiversity.

The field site network around the European LTER Network will consist of about 100-150, sites largely based on existing facilities organised at national level. The network will be developed to provide

representative coverage of the main ecosystem and landscape types and to address a wide range of contemporary and emerging environmental issues (including biodiversity loss, land use change and water quality, carbon budgets, spread of alien species, climate change impacts on ecosystem services, environmental change and human health). The establishment and operational costs of the network will be reduced by making best use of existing sites and organisational structures, although in some regions new sites will be needed. The use of existing sites will also give access to long-term datasets for the assessment of baselines and natural variability and trend detection. In addition, a sub-set of these sites will be established as larger scale (regional) multi-functional research platforms (Long-term Socio-environmental Research (LTSER) sites) in which the data to enable the relationship between natural and socio-economic processes affecting biodiversity will be collected,

Data collected from the sites managed through a smaller network of inter-operable data centres capable of delivering data and information to European and Global research communities. With respect to distributed access and interoperability, the European infrastructure developed in the GBIF context offers a ready to use platform which needs to be adapted to the specific needs of the data centres. This offers the possibility to greatly extend the scope of primary data available to researchers by including the natural history collections and recording communities into the common infrastructure, both providing input of solid taxonomic capabilities to the ecological community and access to current distribution and functional data to systematics.

These components are being brought together as part of the strategic plan to develop a European terrestrial "Biodiversity Observation and Research Network" (BORN), as part of the P6 Network of Excellence on "A Long-Term Biodiversity, Ecosystem and Awareness Research Network" (ALTER-Net).

Biological / geological collections and taxonomic data repositories

Biological collections represent the diversity of nature in a critical selection of specimens which reflect the existing or past (genetic) variation of species in space and time, from geological to anthropological dimensions. Geological collections complement this with specimens which document the evolving abiotic environment of our planet. These collections enable us to reconstruct Earth's history, understand the present, and forecast the future; information that profoundly, and increasingly, affects our understanding and exploitation of the life on this planet. Great strives forward have been made with respect to contributing data on specimens in natural history collections and observation data held by species observation recording organisations and floristic or faunistic mapping schemes. The Global Biodiversity Information Facility unites advanced informatics tools and strategies for global standardisation, networking and common open access to such primary data with the reconciliation and coordination process among stakeholders providing such information. European projects such as BioCASE, EuroCAT (building upon ERMS, Fauna Europaea, and Euro+Med Plantbase), ENBI and SYNTHESYS NA have, in close collaboration, contributed significantly towards GBIF's global aims and have at the same time created a model infrastructure that can be used on the European as well as on national levels. This includes implemented protocols for distributed data access, data exchange standards (developed in collaboration with TDWG) and a comprehensive data portal strategy. This basis for a new infrastructure processing can be expanded to the broader scope of observational data. The prime target remains to overcome the inadequate degree of data mobilisation, i.e. digitisation and standardisation of specimen and data collections, and participation of institutions holding such data. This will be followed by the implementation of data quality assurance measures. Apart of this task is to maintain and regularly update authoritative species lists for the European biodiversity, and also for parts of the global biodiversity if the basic expertise is only available in Europe.

LIFE-WATCH will realise the full potential of taxonomic and collection-based information by bringing the institutions which support taxonomic research and biological collections as components in a comprehensive network, allowing integration and availability of the various kinds of biodiversity information. LIFE-WATCH will also link observations data collected from marine and terrestrial environments with the vast amount of data in physical collections. Such facilities exists in no other form or place, thus providing analysis of the evolution of biodiversity rooted in the past by exploiting the accumulated knowledge. Much of the information of collections indeed was obtained prior to modern development and constitutes an irreplaceable record of past biodiversity, and collections are

the most lasting objective informative data source on changing landscapes and patterns of species distributions. Because taxonomy has been founded and developed in Europe, the EU taxonomic institutions grouped in the CETAF (Consortium of European Taxonomic Facilities) hold altogether the most comprehensive body of specimens and associated taxonomic literature, research and expertise in the world. BioCASE and SYNTHESYS NA provide the models and protocols which make this information, of which only less than 5 per cent is digitised so far, readily accessible and interoperable with environmental data. The contribution of EDIT is not only to coordinate such policies for taxonomic research and expertise and to make the information in the collections available, but EDIT will also prepare the internet platform allowing for collaborative creation of new knowledge and correlative improvement of the availability of new taxonomic data.

Facilities for data integration and interoperability

Direct observation includes the use of satellites and planes connected with a grid of ground observatories covering Europe for measuring a series of standardised and quality controlled biological variables coupled to physical – including geological - and chemical observations. The existing technical protocols developed by BioCASE and integrated into the GBIF infrastructure allow access and retrieval of complex data in the form of XML documents from widely distributed data sources. Data standards and processing facilities have to be developed or improved to link the information from different sources, ranging from collection records to observatory data on terrestrial and marine biodiversity. Information structures and services providing the linking elements such as species, localities, and environmental parameters, as well as data and quality/usability standards are rapidly evolving. In the taxonomic arena, EU-LIFE WATCH would provide a European GBIF component which, focussing on the biodiversity in Europe, provides the services needed to use taxonomic information as an effective tool for broad information clustering. The other primary component, spatial information, has to be developed in close adherence to INSPIRE, making biodiversity information an integral part of the European spatial information infrastructure. Data quality and usability standards, same as semantic definitions of information components have to be driven in global cooperation, for example by supporting the standardisation processes in GEOSS and TDWG.

Virtual laboratories

The wealth of large data sets from the different (genetic, population, species and ecosystem) levels of biodiversity opens up an unprecedented new area of research. Comparative data mining in these data sets allows now for interlinking the different levels of biodiversity and study the existence and the mechanisms behind common patterns. Bio- and ecosystem complexity can be understood by combinations of genes, functions, species and ecosystems together with external factors. Since the number of on-line biodiversity data resources through the Internet is increasing at high pace, now data visualisation, data mining and analysis or predictive modelling techniques require a Grid based approach in a collaborative laboratory environment.

Complex and multidisciplinary problems force scientists to collaborate in virtual organizations at a global scale. Biodiversity e-Science will enable "distributed large scale" science, and increasingly the only way to participate in new developments of science in this area. Biodiversity e-Science is the multidisciplinary scientific approach to address the multitude of questions by organizing information in computer networked collaborations and distributed data sources, and by utilizing new developments in biology, computer science, mathematics and information and communication technology. Such an approach will allow for:

Distributed computing, using capabilities of the Grid to allow for efficient and effective use of CPU by dividing applications into sub-applications that can run on different processors in parallel to speed up the computation process.

High throughput computing and large-scale data analysis, for remote processing and analysis of data, rather than copying these to a single location.

Collaborative computing, for shared use of data and applications together for collaborative working

scientists and groups.

The plan is to provide a Grid laboratory environment for access and computing with the data and facilities of the contributing centres. The architecture will include the following components:

- Making data resources Grid enabled;
- Extension with Grid services (different Globus facilities);
- The Biodiversity e-Science interoperability layer (The challenges are categorised in the following areas: data generation, -management and –fusion; data integration and problem-oriented representation; process modelling and simulations; algorithms for complex systems);
- Adaptation and Integration layer (matching of distributed data and analytical/modelling tools);
- The portal functionalities for users.

Service centre

Although the LIFE-WATCH infrastructure is distributed and virtual by nature, it is essential that users can address a recognisable service centre, which also provides publicity and other dissemination activities. This LIFE-WATCH Service Centre will be established with tasks to:

- advertise the research and other use opportunities to the audiences involved,
- process the procedures to select and admit user groups,
- organise training courses to promote more effective use of the infrastructure,
- operate a fellowship programme including a competitive award scheme for young researchers with original ideas.

Outreach and communication with the wider public and policy will be achieved through a partnership with the European Network of Science Centres (ECSITE), a network of science visitor centres in 25 European countries that currently receive in excess of 30,000,000 visitors per year and provides a unique platform for research on attitudes and understanding related to biodiversity and ecosystems and through the development of an International Press Centre for Biodiversity (IPCB).

5. Further information, including strategic importance to ERA

The LIFE-WATCH research infrastructure will contribute a European component to the GEOSS 10-year implementation plan, particularly in relation to (i) enabling global, multi-system information capabilities for biodiversity conservation; and (ii) improving the coverage, quality, and availability of essential information from the in situ networks and improving the integration of in situ and satellite data. LIFE-WATCH will be unique in its scope and approach but will complement other initiatives around the globe, e.g. NEON [USA], to provide. "A web of sites and sensors taking the earth's pulse". It will therefore be a central component of the European contribution to GEOSS, complementing its remote earth observation data.

6. Identification of other socio-economic impacts

There is quite a number of innovative possibilities arising from the new initiative, and these have been highlighted in the full version. The infrastructure itself is also innovative with its new provisions for

direct links to sites in key ecosystems for quantifying the cause-effect relationships driving changes in biodiversity and ecosystems services, the development and deployment of data-based models for forecasting the impacts of environmental changes and cross-sectoral policies on biodiversity and ecosystem services or for instrumented sites with comprehensive environmental data, providing the European research community with multi-functional research platforms for inter-disciplinary research on biodiversity, ecosystem processes and ecosystem services.

Information and communication technologies offer new, unprecedented opportunities to manage and analyse biodiversity information for specific market and user-group demands, and to develop and offer expert services and products that in return also will create new markets. It will be a fast growing economic sector in the next decades. Clients are of a different nature, and include both public and private sectors. Promising markets are in the several categories like (i) Land-use planning, (ii) environmental assessment, and environmental monitoring; (iii) Nature conservation and management; (iv) Agriculture, trade, health and safety; (v) Natural products, pharmaceuticals, biotechnology; (vi) Overseas development and capacity building.

7. Participating organisations / support from ember states

Support for LIFE–WATCH has been expressed by the organisations participating in the current FP6 NoEs including Terrestrial and Freshwater sites [24 organisations in 17 European countries], Marine sites [78 organisations in 22 European countries] and Major taxonomic data collections [26 organisations in 13 European countries].

The main scientific European networks in biodiversity research, including the most leading institutes Europe support this proposal. The LIFE–WATCH plan was communicated to all these institutes, which also confirmed this support. The international organisation of GBIF is an important partner, since the LIFE-WATCH infrastructure builds upon the GBIF services. At the level of member states, this plan is presented by The Netherlands. Several member state institutes are engaged in research projects, which directly contribute to the construction of LIFE–WATCH [For example: the projects, which design biodiversity information processing and modelling in the GRID-environment; in the UK the BD-World project; in The Netherlands the EcoGRID project].

8. Budgetary information (preparation, construction and operation costs)

All costs below are full construction or operational costs, including housing, administrative and overhead costs.

Preparatory cost (total in M€)	Construction cost (total in M€)	Operation cost (total)	Recommissioning cost (total in M€)
10,50 mln €	368,50 mln €	71,00 mln € per year	Decommissioning costs are not applicable for this infrastructure since it will not have considerable physical parts, such as buildings or large-scale equipment [apart from what will be invested locally by interested member states].
(of which likely to	(of which likely to	(of which likely to	(of which likely to be obtained by

be obtained by possible stakeholders) 20 % estimated national and other contributions	be obtained by possible stakeholders) 74 % estimated national and other contributions	be obtained by possible stakeholders) 50 % estimated national and other contributions	possible stakeholders) 0

9. Timetable

The establishment of the research infrastructure goes through four phases:

- Conception phase [1999 – 2005]
- Preparatory phase [2005 – 2008]
- Construction phase [2008 – 2014]
- Test and operational phase [2012 – 2034]

10. Contact

Wouter Los [los@science.uva.nl]

Faculty of Science - Zoological Museum Amsterdam

Mauritskade 61 1092 AD Amsterdam

http://www.lifewatch.eu/

5. Emerging Proposals for Research Infrastructure

Emerging proposals are the proposals that the Expert Groups consider require further elaboration before they can be recommended for inclusion in later iterations of the Roadmap. They are presented here by Expert Group.

5.1 Genomics, Bio-informatics and related fields

1. Project's name and descriptive title
European Infrastructure for Chemical Biology
2. Short description of project and main characteristics
This infrastructure will incorporate a European Molecular Library Resource Centre (EMLRC) and a European resource for Ligand Binders against the Human Proteome. The EMLRC will involve the Europe-wide coordinated acquisition and collection, maintenance, dissemination, application, validation and information storage of small molecule tools to advance basic research in life sciences. It will contract with chemists to provide unique and special compounds to be included into a central repository for biological activity profiling. It will enhance and promote access to Europe's compound repository and screening technologies for all biologists submitting their biological assays. Data of research projects supported will be collected in a central database of biological activities of chemical compounds made available to the public. This database will be an extremely valuable treasure for future drug development in Europe. It is also fundamentally important to be able to detect, quantify and characterise all relevant human proteins in tissues and fluids in health and disease. A European resource for Ligand Binders against the Human Proteome will require a comprehensive collection of specific ligand-binding reagents against all members of the human proteome. Open access to this resource will be made available to biomedical researchers throughout Europe. The project will involve high throughput production of binders on a large scale, to cover at least 100,000 target proteins, as well as the characterisation, standardisation and description of the binders, together with organisation of storage, access and distribution. The consortium will also use the binder collection to characterise the composition (localisation, function, structure) of the human proteome.
3. Science case (scientific justification, including new areas to be opened)
The biological sciences progress by elucidating underlying mechanisms of complex biological processes. Based on these mechanisms, new principles and means for therapy and intervention are developed. Identification of molecular partners interacting in cellular and organismal processes requires experimental perturbation of such processes, genetically (mutations, etc.) and biochemically (use of agonists/antagonists). The number of available ligands for biochemical studies, however, is rather limited and not adequate to the number of new potential targets emerging from genome research. The chemical biology approach addresses this need by a systematic search for bioactive compounds utilizing large collections of small chemical molecules from various sources, suitable assays to interrogate biological systems, technologies and hardware for high-throughput screening and software for logistics, data storage and analysis. The project aimed at identifying ligand binders against the human proteome will integrate the leading European research groups with complementary expertise in order to assemble the collection of binders, develop applications, establish a major database of their properties and organise means of their storage and distribution with the aim of free access to these reagents by the European biomedical research community.

4. Impact to society and to new technologies for industry

The interdisciplinary chemical biology approach brings together chemists, engineers, informaticians and biologists and creates numerous opportunities for innovation and commerce. Chemical Biology is opening new paths for research in the genome era and its most direct translation into benefits for basic science and for health of the public: chemical compounds are the traditional products for medical therapies and agricultural/ecological management. All industrial branches based on the life sciences will immediately profit from the activities of the EMLRC.

Similarly, a European resource of proteome binding reagents will lead to huge benefits for basic and applied research, healthcare, diagnostics, discovery of targets for drug intervention and therapeutics. It will thus be of great advantage to the research and biotechnology communities. Furthermore, partnerships with industry are envisaged and will be an important part of the project as a large number of SMEs, as well as major pharmaceutical companies, make and use binders extensively in drug development programmes.

5. Strategic importance to ERA

The EMLRC will fulfil similar needs as the Molecular Library Initiative (MLI) of the US NIH road map for health research (Austin et al. 2004 Science 306,1138). Also, the desirability of a comprehensive resource for identifying ligand binders against the human proteome has frequently been pointed out and has been discussed at international meetings, and efforts in this direction are in progress, particularly in the USA. It is very important that Europe does not get left behind in building such a resource. Without coordination, there are likely to be a number of independent efforts at different centres which will inevitably lead to duplication of efforts, lack of standardization, and limited access. FP7 will be the opportunity to put this coordination into practice. In general terms, Europe is already well advanced in the technologies required and excellently placed to initiate this large scale project. The multidisciplinarity and critical mass of expertise required is available in the participants of the Network.

6. Maturity of proposal (including possible timetable)

Performance of high-throughput/high-content compound screens with biological assays requires extensive and expensive infrastructure and equipment as well as special chemical and technical expertise unaffordable for and unnecessary to be implemented redundantly at each of Europe's research laboratories requesting to apply this approach. There are already a few sites in Europe where independently such infrastructure with low to moderate capacity is emerging and offered also to external collaborators. (An example of a related infrastructure is the Cambridge Structural Database (CSD), which is the world repository of small molecule crystal structures. In addition to being a unique international collection, with currently 366,886 structures, it also contains superb software for database access, structure visualisation and data analysis, and structural knowledge bases derived from the CSD. It has been serving the world-wide community since the early 1970s). In Germany a consortium of expert groups has started to coordinate its resources and expertise within a national network (ChemBioNet).

In addition, a first workshop was held in Cambridge (UK) in September to examine the ligand-binders resource and was attended by an EC representative from Brussels. At his suggestion, preparation is under way for a Coordination Action under the current FP6 Infrastructures call, with 28 participating institutions throughout Europe (see below). The proposal will be submitted by March this year. The intention is that this will enable benchmarking, standardisation and forward planning studies to be carried out in preparation for a full FP7 application to establish the resource in 2007. A second workshop to include all the participants in the proposal will be held in Uppsala (Sweden) in June 2005 and will take the network to the next planning stage.

7. Budgetary information (preparation, construction and operation costs)

The establishment and maintenance of the EMLRC requires similar financial support as the US government has allocated for the NIH-MLI (about 80 million € per annum).

A financial request has not been considered in detail yet for the ligand-binders resource, but is likely to be in the region of at least 20-30 million € over 5 years. For comparison, a project focusing only on one part of what this initiative intends was initiated in Sweden with national funding of 25 million € (Wallenberg Foundation).

8. Comments on possible partnerships

This rather young discipline of chemical biology is currently rapidly evolving both on the technological and the application side. Therefore a virtual centre build from a network of national sites of excellence actively involved in research & development will be favourable. There will be three components focused on screening, cheminformatics, and technology development, which are being carried out via EU grant and contract mechanisms.

Currently there are 28 interested partners (universities and research institutions) for the ligand-binders resource, representing most of the leading groups in Europe, including institutions from BE, CH, CR, DE, FI, FR, IRL, NL, SE, UK. Additional contributions will come from collaborators in the USA. The FP6 CA proposal is being coordinated by Dr Mike Taussig (Babraham Institute, Cambridge, mike.taussig@bbsrc.ac.uk).

1. Project's name and descriptive title

European Infrastructure for Systems Biology

2. Short description of project and main characteristics

After two decades of genomic research, many of the molecular components of human cells, including those implicated in disease, have been deciphered or will become available in the foreseeable future. Despite this wealth of data a systems level understanding is still largely missing. The general focus of biomedical research needs to change from primarily a component-by-component analysis at the molecular level to a systems biology level, capturing the characteristic network dynamics behavior, and thus providing a much more comprehensive understanding. This has specific implications to complex diseases, for which the underlying genetic basis is related to combinatorial interactions of multiple genes. This paradigm shift in biomedical research cannot be achieved by a few isolated research teams but requires the establishment of a *European Center for Systems Biology*.

3. Science case (scientific justification, including new areas to be opened)

The last decade saw the advent of novel molecular high-throughput technologies, with a trend of rapid improvement in capacity and sensitivity. These include microarray technologies for expression studies, Single Nucleotide Polymorphism (SNP) discovery and scoring, the recently introduced massively parallel signature sequencing (MPSS) methods as well as lab-on-a-chip technologies, which combine miniaturization and automation. Such technologies have begun to provide an unprecedented amount of data about the state, dynamics and variability of living cells, organs and entire organisms. With more and more data available on DNA, RNA, and proteins and metabolites, creating an integrated picture and reaching a holistic understanding has become possible, but will constitute an enormous task. We need to develop a blueprint of life in health and diseases that should not solely consist of descriptive flowcharts, but must be based on rigorously quantitative data-based mathematical models of metabolic pathways, signal transduction cascades, cell-cell communication, transcription control and the like. As a first steps, a database for genome-wide molecular models of complex diseases (*SysBioDB*) has to be implemented. This database will become as important as present genomic databases. Further, modeling and simulation platforms will have to be provided to the biomedical research community. EUSYB will be responsible for providing these technologies and databases to a very large European and international community of biologists, physicians, bioinformaticians and policy makers.

4. Impact to society and to new technologies for industry

The first high-throughput techniques developed were DNA sequencing methodologies, allowing the sequencing of a large number of genomes from different organisms. Genomics is now moving towards studies of gene expression and function. In the past decade, genomics, proteomics and high-throughput microarray technologies have fundamentally changed science's ability to decipher the molecular basis of cells and tissues in health and diseases, giving us a new and comprehensive view. For example, in cancer research diagnostic opportunities have emerged for tumour classification and prognosis. Metabolomics revolutionise the understanding of transduction and control pathways. To interpret the large amount of data, extensive computational development is required. Soon, the elucidation of biological networks will dominate the scene in Physiology. The massive accumulation of genomic, proteomic and metabolomic

information will be used in computer programs to simulate biologic processes. Bioinformatics has grown to encompass a wide range of fields in biology from gene studies to integrated biology. This is where Systems Biology emerges, aiming to comprehend biological organisms as a whole. In medicine, scientific results and applied biotechnologies arising from Systems Biology will be used for effective prediction of diseases and benefits/risks associated with drugs (pharmacogenetics and pharmacogenomics). Widespread applications for personalised medicine will require associations of gene expression pattern with diagnoses, treatment and clinical data. This will help in the discovery and development of drugs. Despite of two decades of genomic research complex diseases such as cancer and neurodegenerative diseases remain widely not understood on a systems level. The social costs and health care investments for treatment of complex diseases are tremendous. Thus, a *European Center for Systems Biology* is urgently needed in Europe. This is supported by the formation of entire institutions devoted to Systems Biology, e.g. Institute of Systems Biology, Seattle, as well as others in the USA and Japan. Industry will largely benefit from EUSYB since its research will entirely change the way we will diagnose, treat and cure such diseases in the future. Notably,

Systems Biology is seeing an increasing mutual interplay between academia and industry. A relevant example is cutting edge DNA/RNA sequencing technologies such as MPSS, where the original ideas came from academic researchers, technology transfer has taken place to commercial entities, which in turn provide service to academia. This model is becoming increasingly popular as technologies become increasingly sophisticated, making service rather than hardware purchase viable and cost-effective. Thus, it is envisaged that EUSYB will have strong and mutually beneficial links to the biotech industry.

5. Strategic importance to ERA

EUSYB will put Europe in a leading role of postgenomic research in Systems Biology of complex diseases. Comparable to EMBL in molecular biology research, EUSYB has the potential to become the leading Systems Biology center in the world. Importantly, EUSYB will mesh in a highly effective manner with all other ESFRI-recommended research infrastructures, including structural biology, biobank, imaging and bioinformatics.

6. Maturity of proposal (including possible timetable)

All expertise to set up EUSYB exists in various research centers, universities and private companies. This scattered expertise in bioinformatics, biomedicine, mathematics, theoretical physics, and engineering can be readily channeled into EUSYB. The concepts for setting up SysBioDB have been developed and are ready to be implemented and to be deployed.

7. Budgetary information (preparation, construction and operation costs)

For construction and first equipment of *EUSYB* 50 million € are needed. Operating costs including staff require 5 million € p.a. Implementation of SysBioDB will costs 2 million €.

8. Comments on possible partnerships

EUSYB should be located in proximity of European centers in biomedical research. Heidelberg,

Munich, or Berlin, Germany, as well as Cambridge, UK, would be potential candidates.

1. Name and descriptive title

Advanced Light Microscopy for Europe

2. Short description of new RI (or major upgrade) and main characteristics

The goal of this initiative is to establish advanced light microscopy imaging centers in Europe to generate and apply novel advanced technology for non-invasive imaging of biomolecular function in living systems ranging from single cells to model animals. With the explosion in the use of digital imaging techniques in basic research, the funding necessary to establish the required infrastructure and human expertise exceeds considerably both the financial and scientific capabilities of individual laboratories or even of institutions.

The technology developments of today, which are destined to become the routine research instruments of tomorrow, require a complex combination of expertise in areas such as probe development, biosensors, nanotechnology, single molecule imaging, lasers, image detectors, distributed computing, scientific databases. It is apparent that, although such expertise exists throughout Europe, such interaction is unlikely to occur within the current fragmented structure of European imaging centers.

To address the problem of resource fragmentation, the proposed infrastructure will organise distributed but interlinked Integrated Biological Imaging Centers of excellence in nearly every member state, so that all basic science research laboratories would have access to the latest technology and expertise. The establishment of these centers will be aided by discoveries that emerge from different disciplines and are aimed to assist in the development of effective therapeutic agents by monitoring their biological activities.

The requested funding will update and supplement the available equipment in the existing centers, establish such centers in the new EU member states and provide the means for the multidisciplinary Research and Development (R&D) which will bring new innovative technologies and further advance the field.

3. Science case (scientific justification, including new areas to be opened)

A continuing need of biological research is the capacity to follow and record molecular processes, in the context of the living organism. Molecular imaging holds great promise for early detection and treatment of numerous diseases, for providing researchers with detailed information about cellular physiology and function, and for facilitating the goal of personal medicine.

The advent of fluorescent proteins and versatile, chemical fluorescent probes has facilitated the rapid development of modern, cutting-edge fluorescence microscopy methodologies and tools. Available technology today goes beyond simple photography to allow real-time monitoring of biological phenomena, in vivo. In addition to imaging cellular and molecular processes, fluorescence microscopy techniques offer the capacity for analytical measurement of several physiological parameters such as pH, specific ion concentrations, electrochemical gradient potentials, molecular diffusion coefficients, molecular transportation/movement speed and many others. The explosive development of novel fluorescence microscopy techniques has afforded their widespread applications and has rendered them an essential part in the arsenal of modern research tools.

The ultimate goal of biological imaging is to visualise single molecules and their interactions within the context of complex, live biological structures. However, to reach these goals will be necessary to develop new types of tools and instrumentation which can overcome current technical challenges associated with the resolution at this level. Due to the nature of modern imaging needs, these developments will require

advances IN PARALLEL in many collaborating fields: chemistry for probe development, biology, engineering, optics, computing.

While fluorescence microscopy has already opened new vistas in biological research, there is still enormous potential for innovation and optimization. New technologies will be required to study the 3D functional architecture of gene domains in cell nuclei, as the resolution of current optical microscopes is inadequate. Recent resolution improvements such as the spatially modulated illumination microscope, 4Pi confocal microscopy and STED microscopy have provided the first evidence, but further investigation will require novel nanotechnology and single molecule imaging techniques.

Further research is needed for the production of new probes which can combine, in one molecule, more than one sensors to reduce, besides various technical drawbacks of the multiple probe approach, the degree of external impact to the cell. Probe development of this type will have wider implications, possibly used in non-invasive medical diagnostics.

Finally, further development is required for photoactivated and photoswitching probes which have wide applications crossing the boundaries of biology into protein based data storage devices.

Image detectors and lasers is a field that has revolutionised the imaging field the last 10 years. The advent of CCD cameras open new worlds in imaging. Now there is the need for further developments in the areas of signal-to-noise, quantum efficiency and response time to be able to follow the new fast biosensors for live imaging. Electron Multiplying CCD cameras and microchip lasers which allow the miniaturization of two-photon excitation is just the beginning.

A big advantage of the proposed infrastructure will be the efficient use of computing resources. Although a modern desktop computer packs a lot of processing power, the data storage, handling and processing requirements of modern imaging methods surpasses any of those. We could argue that computing places bottlenecks in the use many experimental algorithms on large datasets. However, the speed of networking is currently at an acceptable level with further scope to improve. Therefore, sharing supercomputer resources which could be established in the centers of the network, at national levels, would be both extremely useful and realistic. This arrangement would satisfy the processing and storage needs of imaging, but of course it will be not of much use to basic science, unless the terabytes of data generated can be properly organised and easily retrieved.

The current research on web based Scientific Databases tries to provide a solution. It can be based on some existing open source European initiatives (Open Microscopy Environment OME or Scientific Image Database SIDB). Eventually, the final product should provide a common, but ever expanding and evolving platform, for the linked collection of trusted (therefore must be well maintained) databases encompassing data collection, storage, analysis, annotation. The ultimate purpose is the increased dissemination of the acquired image knowledge across Europe.

4. The Concept case (maturity of proposal)

All expertise required already exists, albeit fragmented, in Europe as part of universities and research centers. Many FP5 and FP6 research projects were put forward because of the need for collaboration with imaging experts and resources. Such projects included 3D vascular imaging (VASCAN), Molecular imaging (MOLIM), genome and its dynamic 3D structure in the cell (3DGENOME), membrane structure resolution (E-MeP) and nanotechnology (NANOMED) to name but a few. All of the imaging resources currently rely on short term funding granted under separate research programs rather than being organised as infrastructure. There are a number of "Network of Excellence" consortia such as in European molecular Imaging (EMIL), in Micro-Optics (NEMO), in Nanodevices (SINANO), network for functional integration (ENFIN) currently funded by the European Commission which could be used as the basis for the proposed infrastructure.

5. Further information, including strategic importance to ERA

One of the main goals on this initiative is for Europe to maintain its competitiveness in the imaging field. The required investment is high and should be in addition to funds allocated to basic research and not part of it. However, the use of such an investment through a coordinated plan, should have significant advantages compared to equivalent funding on the currently fragmented national initiatives:

a) the investment can be more targeted so that the cutting edge technology is not duplicated unnecessarily in each member state
b) the dissemination of know-how and resource duplication or enhancement of infrastructure between collaborating member centers will be more efficient
c) it will facilitate the use of shared resources (algorithms, processing power, databases etc.), a situation that is becoming increasingly feasible with the huge advances in the networked computing.

6. Identification of other socio-economic impacts

Due to the long tradition in optics design and microscopy, European industry is currently in leading position in the production of high caliber optical equipment. However the competition from USA and Japan is growing, especially in the very specialised applications. This is due to their policy to support cutting-edge research in centres of excellence. A recent example is the establishment of seven Centres of cancer nanotechnology Excellence in the USA. For European industry to maintain its leadership, the time from concept to product has to be reduced. The proposed initiative will effectively contribute toward this goal as we envisage very strong ties between industry and the imaging infrastructure. By funding the R&D at imaging centres of excellence, where a multidisciplinary environment will be more readily available than in industry, concept and prototyping will be achieved more rapidly. The industry will be then receiving a prototype closer to the final product, which will significantly increase its competitiveness.

7. Budgetary information (preparation, construction and operation costs)

Preparatory cost (total in M€): **5**	Construction cost (total in M€): **120** Building~20 Imaging centers	Operation cost (total) **75 M**	Decommissioning cost (total in M€)

8. Comments on possible partnerships

The infrastructure should be modeled around the EMBL centres and include at least one promising site from nearly every EU member state.

1. Name and descriptive title

European Infrastructure for Synthetic Biology

2. Short description of new RI (or major upgrade) and main characteristics

A new infrastructure to support synthetic biology in Europe is essential to develop momentum and consolidate progress in this research field which has enormous strategic importance for Europe. The objective would be to provide key service functions to the synthetic biology community, to enable standardisation of biological parts on which synthetic biologists can draw, including the provision of reference methods and materials, as well as associated research and top level training.

A "flagship" infrastructure, as a synthetic biology institute integrating curatorial functions (standardisation, archiving, etc.), research and training, would be a means to spread excellence. In this emerging area, where it is critically important both to encourage creativity and diversity of approaches and at the same time promote standards, such an initiative should function as a leading actor in the field but without dominating the research community.

Such an infrastructure should therefore engage and build on the strengths of already existing infrastructures (e.g. to establish synthetic biology databases in bioinformatics centres or respective biobanks in sequencing centres) and could either be constructed from scratch or by upgrading one or more already existing facilities. In any event, its role should include the networking of existing and future research, training and service facilities. One model could be that of EMBL, allowing national/regional activities to take part by the creation of local "synthetic biology" nodes.

3. Science case (scientific justification, including new areas to be opened)

Synthetic biology is concerned with applying the engineering paradigm of systems design to biological systems in order to produce predictable and robust systems with novel functionalities that do not exist in nature. In its essence it is the logical next step in the post-genomic era. Just as all engineering disciplines maintain a fruitful relationship with the fundamental sciences that underlie them, synthetic biology will seek to use and expand the mechanisms that control biological organisms using engineering approaches. This engineering perspective may be applied at all levels of the hierarchy of biological structures – from individual molecules to whole cells, tissues and organisms. In essence, synthetic biology will enable the design of 'biological systems' in a rational and systematic way.

Where is the area going in the next 10 to 15 years?

The development of synthetic biology may best be compared metaphorically with the development of the computer industry and the impact it had on many industries and businesses. About 30 years ago, only a few companies were involved in the computer industry, and the functions and applications of computing were rather restricted and specialised. However, the application of system engineering design principles such as the development of standardised components for electronic engineering and circuit design – that is, the decoupling of fabrication as such from the exploitation of these parts in complex devices – along with the increasing scope and potential of computer software and a broader view of how the computational capacity of microprocessors might be exploited in technological applications, led to the vast expansion of computers from being centralised data banks and 'number-crunching' machines into devices that are central to everything from process engineering to communications technologies to fundamental scientific research, as well as finding their way into home applications.

In the same way, synthetic biology could also revolutionise the biological and biotechnology industries

and most probably biology as a science. To achieve this, it will be important:

- to invent, construct and test basic parts of complex (semi-)synthetic systems with well controllable, preferably monofunctional, programmable and robust behaviour.
- to invent ways to efficiently integrate parts into complex synthetic systems that will to some extent alter cell biology and provide a cell with novel functions and/or capabilities.
- to develop a common framework for characterizing and standardizing parts.

What is needed most?

Funding is needed both to support fundamental research and training needs and to enable the establishment and maintenance of the infrastructure that synthetic biology requires: for example, an open-source repository for the molecular and genetic components and modules that should form the set of standardised parts on which 'biological engineers' can draw, synthetic biology tools such as DNA synthesis of large oligomers, design software for systematic testing purposes, etc.

Specific requirements for a synthetic biology infrastructure

- Training site for researchers and engineers

The interdisciplinary nature of synthetic biology creates a need for educational initiatives at all levels, from undergraduate to experienced researcher, in order to foster the skills and shared language needed for the discipline to thrive. Specialists in different disciplines will need to develop a working knowledge of each other's *modus operandi*, and in the long term it would be desirable to create a new breed of researchers who are familiar both with fundamental biology and with the methodology of engineering, as well as having requisite skills in areas such as computational sciences (bio-informatics) and chemistry (and chemical biology). This will require integrating synthetic biological concepts into standard educational syllabuses.

- To define sufficiently ambitious biological examples for fundamental or applied research that will drive the development of the field
- To run interdisciplinary research programmes combining biology and engineering and further disciplines, and to further develop tools needed in synthetic biology f. e.:
  - the development of algorithms for a suitable synthetic biology design informatics framework and the development of integrated computer-aided tools for systems analysis and design;
  - the development of tools to in silico design of synthetic circuits, i.e. the simulation of gene networks using different mathematical approximations;
  - the development of complex genetic systems based on pre-defined and standardised parts and smaller systems (e.g. design of complex genetic circuits);
  - the transfer of engineering design paradigms to the protein level (modularity and mono-functionality, organization of hierarchies);
  - the development of tools to create new parts, such as automatic protein design tools;
  - novel measurement parameters and principles (definition of suitable engineering parameters for synthetic biology and ways to measure them);
  - genome sequencing, genomic scale in vitro DNA synthesis (even chromosomes of several Megabases) and genome engineering.
- To host training courses for PhD students, post-doctoral fellows and visiting scientists
- To develop and provide educational and scientific materials to allow the public to use and improve existing standardised biological building blocks (parts, modules, systems, etc.)
- To support the knowledge base in specific countries by specific training programmes (emphasis on linking the training with academic curricula)

- Registry and standardisation

The future development of synthetic biology will require a consistent application of the engineering design paradigm. This implies the need to define suitable standardization procedures for biological parts, and facilities where such parts can be stored and controlled. This curatorial function will be essential for

the success of synthetic biology. In the initial phase, preparatory actions for allowing access to the crucial technology of genomic scale DNA synthesis could be considered.

Specific activities and needs linked to the curatorial role of the infrastructure:

- Database of standardised parts and its further development
- Biobank/repository of standardised parts (DNA, etc.) and its further development
- Development of internationally accepted quality assurance tools for the characterisation of parts
- Validation of standardised parts submitted to the registry
- Setup of approval procedure for submitted parts based on a set of certification guidelines
- Establishing codes of best practice for the use of standardised parts
- Interlaboratory comparison programmes with other synthetic biology registries
- Development of strategies to ensure the free use of parts (public access, open source, etc.)
- Hosting a European/International Synthetic Biology Organisation and providing support to coordination and networking activities
- Archiving and collecting synthetic biology knowledge (data mining, library, etc.)
- General support in knowledge management and IPR
- Setup of an international committee to explore related ethical issues and the possible misuse of the technology, developing strategies and guidelines to prevent it
- Setup of safeguards to prevent the creation and use of potential pathogenic microorganisms and viruses, toxic genes and genetic circuits

4. The Concept case (maturity of proposal)

The proposal is emerging and needs to be developed, however such an infrastructure could either be constructed from scratch or by upgrading one or more already existing facilities. As previously mentioned, it should lever the strengths of existing infrastructures (e.g. to establish synthetic biology databases in bioinformatics centres or respective biobanks in sequencing centres) and its role should include the networking of existing and future research, training and service facilities. One model could be that of EMBL, allowing national/regional activities to take part by the creation of local "synthetic biology" nodes.

5. Further information, including strategic importance to ERA

Synthetic biology is a field with enormous scope and potential. It has the capacity to change quite fundamentally the way we approach certain key technologies, such as medicine and manufacturing, but at this very early stage it is hard even to guess where the most important applications will turn out to lie. However, it can be expected that synthetic biology will create highly generic capabilities for the use of bio-inspired tools and processes that will be applicable in industry and the economy. It is likely that open and public scientific knowledge will be embedded very quickly in an unrivalled set of technological "solutions", representing an arena, which will have vast implications for the ownership and control of intellectual property. It is obvious that Europe should invest in this area, in order to create the necessary intellectual and physical infrastructures, and capture a share of the valuable intellectual property that is at stake.

6. Identification of other socio-economic impacts

To be included

7. Budgetary information (preparation, construction and operation costs)
Construction cost (total in M€): Approx 31M€ Operation cost (total): Approx 3.5M€
8. Comments on possible partnerships
EMBL and other EU member state organisations

5.2 Clinical and Translational Research

1. Name and descriptive title

EIRBI - European Infrastructure for Research in Biomedical Imaging

2. Short description of new RI (or major upgrade) and main characteristics

A number of *in vitro* techniques are now available to biologists for assessing, at the molecular level, the occurrence of abnormal gene expression that accompanies the development of a pathological state. The field of biomedical imaging is challenged to translate these tremendous achievements into early diagnosis and efficient follow-up of therapeutic treatments as well as into developing novel imaging-guided drug-delivery and minimally invasive treatments.

The establishment of European Infrastructure for Research in Biomedical Imaging is essential to this challenge, and will further maintain the competitiveness of European industries and academic institutions in the broad field of imaging.

With EIRBI we propose the development of eight advanced European Research & Training Platforms with strong translational mission in the following fields: design and testing of novel agents and probes, search of advanced cellular and animal models, development of imaging technologies, development of imaging biomarkers, clinical trials in imaging in oncology, cardio-vascular diseases, neurological diseases and minimally invasive image-guided interventions. The identification of the platforms will be made on the basis of the scientific excellence and the support from the hosting Country.

3. Science case (scientific justification, including new areas to be opened)

At present, *in vivo* diagnostic systems basically assess the structure and function of human organs. Therefore, for important diseases like cancer and cardiovascular pathologies, but also diseases of the central nervous system, only the late symptoms are detected. It is expected that the advances in genomics and proteomics and visualization of alterations at molecular and cellular level will have a tremendous impact on early detection and characterization of disease, and evaluation of treatment as well as the set-up of innovative procedures in the field of image-guided therapies. Furthermore, the molecular imaging approach will have also a major impact on the development of new pharmaceuticals, and the development of this field will increase the availability and "speed to market" of new drugs. EIRBI intends to contribute to the build-up of the European Research in the field of Biomedical Imaging by networking the most qualified groups devoted to i) attain an accurate visualization of the molecular and cellular processes by developing novel probes; ii) develop innovative approaches to image formation and acquisition; iii) integrate imaging modalities, diagnosis and treatment selection by developing bioinformatics of data modelling, correlation and quantitative analysis; iv) pursue innovative procedures based on image-guided drug delivery, cellular therapies and minimally invasive interventions.

The aim of EIRBI is to sustain multidisciplinary projects that, by integration of chemists, biologists, physicists, imaging technologists and clinicians, tackle the most challenging problems in the field of oncology, cardiovascular and neurological diseases in order to give Biomedical Imaging the possibility to express all its potential in human health care.

4. The Concept case (maturity of proposal)

EIRBI will be equipped with the most advanced instrumentation in all imaging modalities of medical interest and it will be endowed with the capability of developing suitable molecular probes as well as the proper cellular and animal models for addressing the study of a given pathology. EIRBI will be linked to EATRIS (the European Advanced Translational Research Infrastructure in Medicine) and the Network of Distributed Infrastructures for Clinical Trials. Also to the existing Large Scale Facilities in the Physics world to grasp new ideas for the development of novel, innovative imaging procedures and with the Bioinformatics resources Infrastructure for accessing to the most efficient procedures for processing the acquired imaging data.

Particular attention will also be devoted to integrate the activities of EIRBI with the European initiatives in the field (EMIL- and DiMI-NoEs and MI-Integrated Project) and with the major scientific associations in the field. Each Research &Training Platform will establish alliances with industrial partners in the field of Imaging Technology and in the field of Imaging reporters manufacturing companies.

EIRBI will be coordinated by a Steering Committee appointed by the participating Member States, supervised by an International Scientific Advisory Board with representatives from the major European industries in the field of Biomedical Imaging. The implementation of EIRBI will take place in three stages:

1. Implementation of the joint programme of activities of the eight Research & Training Platforms around the selected Centres.

2. Consolidation of the ”clustering” process of the Research & Training Platform and of all the infrastructure through the involvement of other qualified research institutions through open calls in order to recruit the complementary skills necessary to guarantee the full operational activities of the Platforms.

3. Stage 3 will complete the fully integrated operational scheme of the whole infrastructure including the launch of calls to select the priority lists of the main EIRBI projects and the support to talented young researches.

5. Further information, including strategic importance to ERA

Traditionally, the European industry has held a worldwide leadership in the field of Imaging Technologies [Philips (NL), Siemens (D), Schering (D), Amersham (UK), Bracco (I), Guerbet (F)]. EIRBI will be very important to keep this leadership.

6. Identification of other socio-economic impacts

An improved health care to European citizens will translate in economical advantages for the society, and the discovery of new products, new equipments, and new diagnostic and therapeutic procedures will represent important incomes for the involved institutions. The health care market is growing fast and the activities that will be carried out at EIRBI are expected to yield a marked increase of the European IP in the field of innovative diagnostic methods and related fields. In particular, EIRBI will have a very active policy for training researchers to pursue the protection of the results coming from their research projects.

7. Comments on possible partnerships

The European Biomedical Imaging community has a number of highly qualified centres that can be considered as excellent candidates to be part of the starting group of the Research and Training Platforms of EIRBI. Moreover some countries have already proceeded with the selection of Centres of Excellence in various fields of Biomedical Imaging.

8. Budgetary information (preparation, construction and operation costs)

Preparatory cost (total in M€)	Construction cost (total in M€)	Operation cost (total)	Recommissioning cost (total in M€)
5 M€	250 M€	300 M€	Not Applicable
(of which likely to be obtained by possible stakeholders)	(of which likely to be obtained by possible stakeholders)	(of which likely to be obtained by possible stakeholders)	(of which likely to be obtained by possible stakeholders)
2,5 M€	200 M€	200 M€	

9. Timetable until operation

Centres will be constructed and fully operational within a period of 3 - 5 years: individual dates will depend on local conditions.

Preparatory phase	Construction phase	Operation	Decommissioning
2007	2008-2010	Starting 2010-2012	

10. Contact

Prof. Gabriel P. Krestin, MD, PhD

Dept. of Radiology

Erasmus MC, University Medical Center Rotterdam

Chair of the Research Committee of EAR, g.p.krestin@erasmusmc.nl

1. Name and descriptive title

High security laboratories for emerging and zoonotic diseases and threats to public health

2. Short description of new RI (or major upgrade) and main characteristics

Creating and reinforcing a European network of L3 and L4 high security laboratories for European infectious disease research.

3. Science case (scientific justification, including new areas to be opened)

Global infectious diseases including HIV, tuberculosis, malaria, leischmaniasis, SARS, BSE, foot and mouth disease and viral haemorrhagic fevers such as Ebola and others are a major burden on socio-economic development in the South, and through migration and global travel increasingly threaten the population of Europe as well. Recent crises have shown that infectious diseases are far from being eradicated in humans as well as animals. One of the key issues to address in order to protect human health is the boundary between human and animal pathogens. The scientific challenges are enormous but the biotechnological revolution allows for important breakthroughs to be made. Diagnosis, surveillance and research of such diseases and their agents require high-security laboratories (containment level L3 and L4).

4. The Concept case (maturity of proposal)

The health sector is one of the main economic sectors and large investments are made to fight diseases on a global scale. Infectious disease control is one of the main challenges and there is a continuous need for new drugs, vaccines, and diagnostics. Substantial developments based on basic and applied research can be expected.

5. Further information, including strategic importance to ERA

The safety and quality regulations for these high security laboratories have become ever more restrictive and require very large investments. National European efforts remain fragmented and diverse, in size as well as in quality. A European coordinated network of high-security multi-species facilities, harmonisation and coordination would greatly reinforce the European capacity. Europe is strong in this area of health research and needs a concerted effort to provide excellent and safe facilities for the European research community.

6. Identification of other socio-economic impacts

The socio-economic challenges for Europe due to larger and more serious outbreaks of infectious diseases may be very dramatic. It is vital to develop Europe's capacity to combat such

epidemics, to contribute to its multi-lateral aid programmes, to train future world leaders in research into infectious diseases and to support the European pharmaceutical industry in developing new diagnostics and therapies.

7. Comments on possible partnerships

First draft to be further developed through existing institutional networks. At the outset, contacts will need to be made to European and national authorities (national boards of health, WHO, military, security etc.)

8. Budgetary information (preparation, construction and operation costs)

Construction cost (total in M€): €22m

Operation cost (total): €1m per year

9. Contact

Dr. Hervé Raoul
Co-Director
Laboratoire P4 INSERM, Lyon

5.3 Biodiversity and the Environment

1. Name and descriptive title

European Infrastructure for the Analysis and Experimentation on Ecosystems (ANAEE)

2. Short description of new RI (or major upgrade) and main characteristics

Continental biosphere plays an important role on global change of the planet by mean of its interactions with atmosphere and hydrosphere and also by the fact that most of the continental ecosystems are subjected to severe manipulations through human activities. Predicting and mitigating the consequences of these global changes is a major challenge for ecologists and agricultural scientists as well as socio-economists. Theoretical and mechanistic models, powerful 'ecosystem analysers' and long term field experimentations are all needed to analyse, model and predict the consequences of global changes on biogeochemical fluxes and biodiversity. These tools need an integrated, strong and innovative development in a concerted way across Europe. This is the objective of the Infrastructure for the Analysis and Experimentation on Ecosystems (ANAEE).

Ecotrons - Understanding the interactive effects of environmental factors on ecosystem functioning requires the capability to simultaneously i) impose specific environmental conditions, ii) measure accurately the main fluxes, and iii) analyse the associated changes in biodiversity and physiology of organisms. Ecosystems in Ecotrons can be seen as model systems half way between mathematical models and the full complexity of nature. Reconstructed, simplified ecosystems can be used to test hypothesis on the link between structure and function, or on the impact of complexity on ecosystem dynamics. Intact blocks of ecosystems cut out of nature can be used to test interactions between environmental factors or to close the balance of cycling elements. Environmental simulations will concern primarily climatic, atmospheric and stress conditions, but other changes could also be simulated by choosing or manipulating the ecosystems to be inserted in the equipment. State of the art instrumentation will allow new breakthrough by removing technical barriers.

Long term field experimental platforms (LTEEP) - For the global changes that can be easily manipulated in the field, it is of the foremost importance to set up LTEEP on selected sites that would encompass of the main European ecosystems or agro-ecosystems and a wide range of climate and soil conditions. Experimental manipulations corresponding to land use scenarios are of primary interest because not only they correspond to one aspect of global changes, but they also constitute management tools for restoring and enhancing environmental conditions, in particular biodiversity. Such a network of experimental site will constitute a large-scale European-Field Laboratory with the aim of providing fundamental, mechanistic information on ecosystem structure, function and resilience. Five thematic areas are concerned: 1) the patterns and controls of primary productivity, 2) the spatial and temporal distribution of representative populations of plants, animals and microbes, 3) the distribution and dynamics of organic matter in soil, water or sediments, 4) the patterns of inputs and movements of inorganic nutrients and chemicals through the ecosystem, and 5) the patterns and effects of disturbances.

Analytical, modelling and bioinformatics facilities - Hypothesis testing as well as system biology approaches to ecosystem science are highly constrained by our analytical capacities. Routine quantitative analysis at a very high throughput of all components of ecosystems is crucial to the development of ecosystem science and is complementary to the experimental components of the infrastructure. The research conducted in ANAEE will involve laboratories at the cutting edge of analytical methods. The opportunity to develop high throughput analysis platforms similar to the one found in molecular biology will be evaluated. New technologies are now available for the development of *in natura* sensors and instruments, which can provide valuable information on organisms and ecosystems biology. An Instrumentation Centre will be build to position Europe at the cutting edge of monitoring organisms and ecosystems functioning. It is also crucial to develop theoretical frameworks and simulation models to help interpreting the results of the Ecotron and LTEEP and to suggest new experiments. The information gained

from this research will also feed scenario simulations to evaluate environmental hazards and impacts on functional biodiversity resulting from a wide range of contrasting land use and management systems. The results of the research programs carried within ANAEE must feed a common integrated data base and information system allowing exchanges and communication between different research teams of different disciplines. The handling and the exploitation of the considerable data as well as the high level of complexity generated by the large number of interactions and feedbacks operating in ecosystems require a large investment in computing power and informatics and the support for the development of an innovative systems biology approach to ecosystem science. A European (Eco) Systems Biology Centre will be built, which will also operate a Virtual Institute for Theory and Modelling.

3. Science case (scientific justification, including new areas to be opened)

The scientific objective of this new integrated research infrastructure is the analysis of the responses of ecosystems and organisms to current and future environmental changes. It aims at providing the scientific community, policy makers, and society with the knowledge and predictive understanding necessary to conserve, protect, and manage European ecosystems, their biodiversity, and the services they provide. There is a need to understand how individual and combined drivers of change affect ecosystems biogeochemistry through altered performances of the different trophic levels. Performances will be altered through modifications of physiological activities of individuals as well as changes in biodiversity. Feedbacks between ecosystem response and global change drivers are also of fundamental importance. With regard to the response of biogeochemical cycles to global changes, a challenging aspect to be addressed is the strong interactions between atmospheric forcings, temperature, CO_2, precipitation and N deposition. Their simultaneous impacts have to be studied by combining experimentation and modelling. The fundamental strength of ANAEE is the coupling of in silico, in vitro and in natura experimental approaches. That will allow not only to provide fundamental knowledge on the processes by which ecosystems, communities and populations of organisms respond to forcing variables, but also to test the validity, the relevance and the importance of these processes in natural situations and to derive valuable predictions and simulations of prospective scenarios. It has always been a strong objective in the designing of the ANAEE to make it relevant for a large array of research questions. This flexibility is a requisite for this infrastructure to be suitable for, or even to stimulate, innovative approaches and to give it a chance to remain relevant for the environmental questions of the next decades. By offering instrumentation to a large range of scientists, ANAEE will have the capacity to stimulate exchanges of concepts and techniques between these fields and to provoke the emergence of new research approaches. So it is essential that information system facilities allowing data base management and shared modelling activities would be associated to ANAEE.

4. The Concept case (maturity of proposal)

Coordinating biodiversity and ecosystem research in Europe is on the way. It will require additional efforts within FP7 to integrate these two aspects of ecological and environmental science. Some coordination needs to be developed between ANAEE and complementary projects of European infrastructures.

Ecotrons - While European research is actively developing in situ facilities to monitor ecosystem fluxes through the eddy correlation technique, there are only a few facilities designed to manipulate environmental conditions on ecosystems. Confined systems designed for plant research (phytotrons) exist in many universities and research centres, but few have been designed for the study of ecosystems. Among them, a few with long-term sustainability received international recognition, while most of them were built for local and temporary use. A new facility, the Montpellier European Ecotron is being built. It will have experiments running simultaneously at three scales with 12 to 24 units per scales and is planned to have state of the art instrumentation for fluxes measurements. ANAEE will help developing the existing Ecotrons and will contribute to the building of a couple complementary facilities. ANAEE will also network these facilities. The contacts existing between some of them (Silwood Park, Montpellier, the ESPAS plant-soil system of

Wageningen, the Paris project …) need to be extended to other existing or planned facilities.

LTEEP (about 30) are planned to be located on the main land use systems in Europe covering a large variety of soil and water conditions across the main European climates. These platforms will be connected with the LTER network established since 20 years in USA and under development in most European countries. Each of LTEEP could have its own scientific objectives, experimental design and monitoring and measurement technology according to its local site specific conditions. Nevertheless a common core of investigations and methods should be established across the platforms. Large field plots will be subjected to different anthropogenic management treatments leading to manipulation of some well identified forcing variables…. All the data recorded on a given LTEEP will be put into a data base system largely open to the European scientific community. Some field plots could host more analytical field investigations for studying more precise *in situ* processes with the help of more sophisticated methodology. So the LTEEP could host for a given time some external research teams, and offer them not only some logistic facilities but also the great advantage of a quasi exhaustive description of the history of the system investigated.

Analytical, modelling and bioinformatics facilities - For most research programs, the involved laboratories often from different disciplines bring their own relevant scientific expertise for sample analysis, data interpretation and modelling. Such a functioning has to be maintained, but could be improved by giving access to specific analytical facilities is needed. Modelling activities are in a great need of coordination and development and ANAEE should play a large role in this domain. Systems biology and ecoinformatics are very much in their infancy.

5. Further information, including strategic importance to ERA

Research on ecosystems in Europe is very fragmented according to the different types of land use, different disciplines and different approaches. This only successful integration so far concerns the European assessment of carbon emissions with the use of a network of eddy correlation towers. A parallel complementary integration needs to be done to integrate biodiversity, climatic and land-use changes. The acquisition of knowledge and predictive capacity on ecosystems functioning and dynamics is strongly linked to our capacity to integrate the currently spread efforts. Too often, for example, N cycle is being investigated in one site, C cycle in another one, and vegetation dynamics and herbivory elsewhere. Disciplinary researches need to complement each other on given sites to understand the complex interactions between environmental factors and between ecosystem components, and a range of sites with comparable approaches need to be set up to reach syntheses that will allow extrapolating across the European continent. The choice of a limited number of Agro-Ecosystems to be investigated at the European level within the LTEEP has to be coordinated with the US and European network of LTER. Such integration will have should have a structuring effect on the organisation of Ecology-Agronomy-Forestry Sciences in Europe. It will also be a necessary step to foster the development of a European ecological engineering which will be needed to counteract some aspects of global or local environmental changes. The networking of Ecotrons, a coordinated grid of LTEEP and the establishment of virtual Ecoinformatics centres are all needed, but none would individually reach fully its goal.

6. Identification of other socio-economic impacts

The development of ANAEE will also strongly contribute to reduce the differential access to research infrastructures across European researchers. Large Ecotrons can only be built in a few countries. ANAEE will make them accessible to all European researchers and research programs. LTEEP can be set up in any countries and will be spread all across Europe. Their networking will contribute to the scientific integration of most European nations. Finally, training of researchers and students will be fostered through this infrastructure and the associated research programs. Specific actions in that direction will have to be incorporated in the submitted proposals.

7. Comments on possible partnerships

Several nations already committed themselves to fund significantly components of ANAEE. France for example invested 4 M€ in the building of the Montpellier European Ecotron. A networking of the individual nation's initiatives through ANAEE will be a strong incentive to increase these commitments.

8. Budgetary information (preparation, construction and operation costs)

The provisional budget is constructed on the basis of setting-up or implementing 10 Ecotron facilities, 40 LTEEP,2 Instrumentation and 2 Eco-informatics Centres. The list of the facilities to be included is not yet finalised. An estimated average cost is taken for the calculations.

Preparatory costs: Meetings of country representatives to coordinate the general scientific and technical development of the infrastructures and their final location: 80 K€; Feasibility studies: 920 K€ (Ecotrons 8x 40 K€; LTEEP 40 x 10 K€; Instrumentation Centre 100 K€; Ecoinformatics Centre 100 K€)

Construction costs: Ecotrons: construction and instrumentation of novel facilities and implementation of new ones: 40 M€ (10 x 4 M€); LTEEP: sites setting-up and instrumentation 40 M€ (40 x 1M€); Analytical facilities (up-grading and labelling of existing laboratories and Instrumentation Centre: 9 M€; Eco-informatics Centre and Virtual Institute for Theory and Modelling 10 M€

Operation costs: Ecotron: 12 M€; LTEEP 6 M€; Instrumentation Centre 2 M€ ; Ecoinformatics Centre 2 M€

Facilities	Preparatory cost (total in M€)	Construction cost (total in M€)	Operation cost (total in M€)	Decommissioning cost (total in M€)
Ecotrons	0.350	40	12	Not applicable
LTEEP	0.430	40	6	
Instrument./Ecoinformatics Centres	0.220	19	4	
Total	**1**	**99**	**22**	
(of which likely to be obtained by possible stakeholders)	0.9	89.1	19.8	

9. Timetable until operation ~1 page

Some components of ANAEE for which individual nations committed themselves are already in operation or will be so within the next 2 years. The time table below for the construction phase does not include them. For operation, the start corresponds to the beginning of a coordinated activity of at least part of the components.

Facilities	Preparatory phase	Construction phase	Operation
Ecotrons	2007-2008	2009-2012	2009 -
LTEEP	2007-2008	2009-2010	2009 -

Instrument./Ecoinformatics Centres	2007- 2009	2010-2013	2009 -

10. Contact

CNRS/INRA France,

Jacques ROY CEFE-CNRS

34293 Montpellier Cedex 5,

jacques.roy@cefe.cnrs.fr

tel 33 4 67 61 32 39

Glossary

ANAEE	Infrastructure for the Analysis and Experimentation on Ecosystems
BEEG	Biodiversity and Environment Expert Group
BMS RWG	Roadmap Working Group for Biological and Medical Sciences
ECBIO	European Centre for Biodiversity Information
EGCT	Expert Group on Clinical and Translational Research
EGGB	Expert Group on Genomics, Bio-informatics, Animal Resources, Systems Biology and Chemical Biology
EIRBI	European Research Network in Biomedical Imaging
EMBIODS	European Marine Biodiversity Data System
EPBRS	European Strategy for Biodiversity Research
EU-BIODOBS	Unravelling Bio- and Eco-complexity; an up-dated extended version of this proposal has also been submitted "Biodiversity databases and observatories for European Research"
GBIF	Global Biodiversity Information facility
GERMPLASM	Center for Genetic Resources Preservation of Animal and Plant
HSS RWG	Roadmap Working Group for Humanities and Social Sciences
IAEE	Infrastructure for the Analysis and Experimentation on Ecosystems
IAGOS-ERI	Integration of routine Aircraft measurements into a Global Observing System – a European Research Infrastructure
LIFE-WATCH	e-Science and Technology Infrastructure for biodiversity data and observatories
PLASMED	Global service Platform on Sustainable Management and Enhancement of Agro-Ecosystems in the Mediterranean
PSE RWG	Roadmap Working Group for Physical Sciences and Engineering
RECIMSE	Establishment of a Resource Centre for Industrial Micro-organisms in the South-Eastern European Countries

Appendix A List of members of the BMS RWG

Chairperson – Ruth Barrington

Scientific Advisor – Fotis Kafatos

Secretary – Brendan Curran

Country	Name	Address
Austria	Kurt Zatloukal	Medical University Graz Auengruggerplatz 25 A-8036 Graz, Austria
Belgium	Muriel Moser	Faculte des sciences, Universite Libre de Bruxelles UULB CP 300 Rue des Professeurs Jeener & Brachet 12 6041 Charleroi (Gosselies) Belgium
Czech Republic	Jan Marek	Government Office Secretariat of R & D Council Prague 1, CZ-118 0a Czech Republic
Denmark	Liselotte Hoejgaard	KF 44011 Rigshospitalet, Blegdamsvej 9 DK-2100 Copenhagen Denmark
EC Representative	Timothy J Hall	DG – Research (CDMA 2/173) European Commission B-1049 Brussels Belgium
Finland	Taina Pihlajaniemi	University of Oulu

		PO Box 5000 FIN-90014 Finland
France	Andre Syrota	CEA / Fontenay-aux-Roses 18 Route du Panorama BP 6, 92265 Fontenay-aux-Roses Cedex, France
Germany	Eckhart Curtius	Referat 613/Lebenswissenschaftliche Forschungseinrichtungen Heinemannstr 2 53175 Bonn, Germany
Greece	George Kollias	Biomedical Sciences Research Center 34 Al. Fleming Str, 166 72 Vari Hellas, Greece
Hungary	Gabor Szabo	Institute of Experimental Medicine 1083 Budapest Szigony u. 43, Hungary
Iceland	Hakon Gudbjartsson	VP Informatics, deCODE Genetics Inc. Strulugata 8, 101 Reykjavík
Ireland	Maurice Treacy	Science Foundation Ireland Wilton Place Dublin 2, Ireland
Israel	Joel Sussman	Weizmann Institute of Science Rehovot 76100 ISRAEL
Italy	Ivano Bertini	Magnetic Resonance Center – University of Florence Fia L. Sacconi, 6 – 50019 Sesto Fiorentino,

		Italy
Lithuania	Gintaras Valincius	Mokslininku 12 LT-08662 Vilnius Lithuania
Netherlands	Frans M Martens	Netherlands Organization for Scientific Research, Director Earth & Life Sciences PO BOX 93510 2509 AM The Hague, Netherlands
Norway	Hans Krokan	Dept of Cancer Research & Molecular Medicine, Faculty of Medicine Norwegian University of Science & Technology 7489, Trondheim, Norway
Poland	Jerzy Duszynski	Nencki Institute of Experimental Biology Polish Academy of Sciences Pasteur 3 Street, 02-093 Warsaw Poland
Portugal	Pedro Simas	Faculdade de Medicina Universidade de Lisboa Av. Prof Egas Moniz 1649-028 Lisboa, Portugal
Slovenia	Irena Mllinaric Rascan	Faculty of Pharmacy, University of Ljubljana Askerceva 7, SI-1000 Ljubljana Slovenia
Spain	José López Carrascosa	CNB – CSIC Campus de la Universidad Autónoma de Madrid Cantoblanco, 28049 Madrid Spain

Sweden	Hakan Billig	The Swedish Research Council SE 103 78 Stockholm Sweden
Turkey	Kemal Baysal	Scientific & Technical Research Council of Turkey RIGEB PK 21, Gebze, Kocaeli 41470 Turkey
United Kingdom	Alf Game	Biotechnology & Biological Sciences Research Council (BBSRC) Polaris House, North Star Avenue Swindon SN2 1UH, UK

Appendix B Biographies of members of the BMS Expert Groups

- Expert Group on Genomics, Bio-Informatics and related fields (EGGB)

Dr Tim Hubbard, Head of Human Genome Analysis, Wellcome Trust Sanger Institute, UK

Tim Hubbard is responsible for bioinformatics groups carrying out analysis and annotation of vertebrate genome sequence produced at the Wellcome Trust Sanger Institute, which was responsible for determining a third of the human genome sequence. He is joint head of the Ensembl genome annotation project (http://www.ensembl.org), which is one of the world's leading database and access point for the human genome sequence. He is also responsible for the efforts of the Sanger Havana group to manually curate the geneset of the human, mouse and zebrafish genomes and the Vega database. Outside genomics he is a co-founder of the SCOP structural classification of proteins database and has been a co-organiser of the CASP structure prediction competition since 1996. He is chair of the RIKEN Genome Sciences Centre scientific advisory council, and a member of advisory boards for the ZFIN model organism database and the UCSC genome browser project (NIH). He is a member of the UK Medical Research council College of Experts and their Informatics Advisory Group (IAG).

Professor Doron Lancet, Director of National Center for Genomics, Israel

Doron Lancet studied chemistry and immunology in Israel, and had postdoctoral training at Harvard and at Yale, USA. At the Weizmann Institute of Science he headed the Department of Membrane Research, and is now Professor at the department of Molecular Genetics, and Director of Israel's National Center for Genomics. He discovered the molecular basis of smell transduction, and currently studies the genomics and population genetics of human olfaction. In the realms of bioinformatics and systems biology he developed GeneCards, a widely used web-based gene compendium, and does research in proteomics, transcriptomics, medical genetics and prebiotic evolution.

Professor Dino Moras, Head of the Structural Biology Laboratory at the IGBMC (Illkirch), France

Dino MORAS, is the head of the Structural Biology Laboratory at the IGBMC (Illkirch) and the founder of the biological crystallography laboratory at the Institute for Molecular and Cellular Biology of CNRS (Strasbourg 1980). His major contributions concern the molecular mechanisms controlling the expression of genetic information. His main results are: (i) the partition of aminacyl-tRNA synthetases in two classes, based on structural and functional correlations. This discovery has had profound implications on our approach of the origin of the genetic code and its evolution, (ii) the first structure determination of a class II complex and the elucidation of the mechanism of aminoacylation in the aspartic acid system. (iii) the first crystal structures of the ligand binding domains of two nuclear receptors of retinoids (RXR and RAR) in their apo and liganded form respectively. (iv) the crystal structures of the vitamin D receptor (VDR) and orphan receptors ROR, ERR and NGFIB. He presently studies the structures of functional transcription regulation complexes in order to elucidate the molecular mechanisms of control. For that purpose he implemented the tools of structural proteomics in the laboratory.

Awards

- Bronze Medal, CNRS, 1972, silver Medal, 1982

- French Academy of Sciences, Corresponding Member, 1987

- European Molecular Biology Organization (EMBO) member, 1987-

- American Academy of Arts and Sciences, member, 1998-

- French Academy of Sciences, Member, 2000-

Professor Mary Osborn, Max Planck Institute for Biophysical Chemistry, Göttingen

Mary Osborn is a cell biologist who has made her career in three countries: the UK, USA, and Germany. She is a scientist at the Max Planck Institute for Biophysical Chemistry in Göttingen and an honorary professor in the medical faculty at the University of Göttingen. Her work has used a variety of proteomic, immunological and microscopical techniques and is focussed on cytoskeletal and nuclear proteins in animal cells. Antibodies from her laboratory have found wide use as cell type specific markers in human cytology and pathology. She holds an honorary doctorate from the Pomerian Medical Academy in Szczezin. She won the Meyenburg Prize and the 2002 L`Oreal/UNESCO Prize for her work on the cytoskeleton. She was a trustee of the Swedish Foundation on the Environment, MISTRA, and has chaired both the Scientific Advisory Board of the European Molecular Biology Laboratory in Heidelberg, and the Cell Biology Section of Academia Europaea. From 2003-2006 she was the President of the International Union of Biochemistry and Molecular Biology (IUBMB) an organisation that represents biochemists and molecular biologists in 72 countries.

Professor John Sulston, Vice-Chair of the UK Human Genetics Commission

John Sulston, FRS, graduated from the University of Cambridge in 1963, took a PhD in 1966, and was then a postdoctoral researcher at the Salk Institute for Biological Studies. In 1969 he moved to the MRC Laboratory of Molecular Biology. There he worked on the biology of the nematode, *Caenorhabditis elegans*, studying particularly its cell lineage and its genome. A collaboration between his group and that of Bob Waterston (Washington University, St Louis) produced one of the earliest genome maps, and in 1990 they went on to sequence it, completing the task in 1998 - the first animal genome to be sequenced. Concurrently he became involved in the Human Genome Project, as founder director of the Wellcome Trust Sanger Institute from 1992 to 2000. The Institute is devoted to genomic studies in a variety of model organisms and parasites as well as human. He is now Vice-Chair of the UK Human Genetics Commission.

Honours include membership of EMBO, the Darwin Medal of the Royal Society, and, jointly with others, the W. Alden Spencer prize, two Gairdner awards, the Rosenstiel award, the General Motors Sloan Prize, the Dan David Prize, and the Nobel Prize in Physiology or Medicine.

Professor Glauco Tocchini-Valentini, Director of the Italian National Research Council's Institute of Cell Biology (CNR-IBC), Rome

Since 1980, G. Tocchini-Valentini has been Director of the Italian National Research Council's Institute of Cell Biology (CNR-IBC) in Rome. Since 1998 he has co-ordinated the organisation of the new international scientific Campus "Adriano Buzzati-Traverso" at Monterotondo (Rome, Italy), which was created thanks to a CNR project that has involved also the most important European scientific organisations. The Monterotondo Campus was created by the CNR for the purpose of developing and internationalising Italian biological and biomedical research, and is named after Prof. A. Buzzati-Traverso, the scientist who, while working for the CNR, brought modern molecular biology to Italy. The CNR transferred the IBC from Rome to the Monterotondo Campus, where research teams work in close collaboration with the international institutions located in the Campus: the EMBL (European Molecular Biology Laboratory), the EMMA (European Mouse Mutant Archive) and ICGEB (Intern. Centre for Genetic Engineering and Biotechnology).

He coordinates the EMMA (European Mouse Mutant Archive) project contracts, supported by the European Union Framework Programmes and he leads the IBC teams participating in several European Networks, Consortia and Integrated and Coordination Actions

Professor Gertjan Van Ommen, Head of the Department of Human Genetics of Leiden University Medical Center (LUMC) and founder of the Leiden Genome Technology Center, The Netherlands

Prof. dr. Gert-Jan B. van Ommen**,** PhD, (1947) is head of the Department of Human Genetics of Leiden University Medical Center (LUMC) and founder of the Leiden Genome Technology Center (LGTC), a principal genomics facility in the Netherlands. He has as major research interests neuromuscular and neurodegenerative diseases (with a focus on Duchenne Muscular Dystrophy, DMD, and Huntington Disease); development and application of genome research and diagnostic technology for disease study, diagnosis, therapy and prevention, including the societal aspects of genetic advances. Members of his department have contributed to the finding of the gene defectis and disease mechanisms underlying Duchenne Muscular Dystrophy, Huntington Disease, Polycystic Kidney Disease, Facioscapulohumeral muscular dystrophy, Hereditary Neuropathies, Fragile X, Rubinstein-Taybi Syndrome, Familial Hemiplegic Migraine, Episodic Ataxia. He has pioneered the development of several mapping techniques, generating the first megabase map of a human gene (DMD), and of mutation detection techniques, including the development of multicolor FISH for cytogenetics and the Protein Truncation Test (PTT), which is now widely used in cancer diagnostics.

Professor Van Ommen is past president and vice president of HUGO (1998-2003), the European Society of Human Genetics (2002-2004) and the Dutch Society of Human Genetics (1993-2000) and Editor-in-chief of the European Journal of Human Genetics (1997-present). He is present and past member of several National, EU and HUGO committees in the fields of Genetics, Innovative Health Care, Genomics, Bioinformatics, Ethics and IP aspects. He is the Director and Principal Investigator of the Center for Medical Systems Biology (CMSB), one of the four Centers of Excellence established in 2003 by the Netherlands Genome Initiative. The CMSB is a joint activity of Leiden University Medical Center, Leiden University, Free University Medical Center and Free University in Amsterdam, TNO Leiden and Erasmus MC Rotterdam, aiming to improve diagnosis, therapy and prevention of common diseases and rare variants thereof.

Professor Taina Pihlajaniemi, Scientific Director of Biocenter Oulu and Head of Department of Medical Biochemistry and Molecular Biology, University of Oulu, Finland

MD in 1982 and PhD in 1987 from the University of Oulu, Professor of Medical Biochemistry, University of Oulu 1990-, Chairman of Medical Biochemistry and Molecular Biology, University of Oulu 1991-, Scientific Director of Biocenter Oulu 1996-, Vice Director/Director of the Collagen Research Unit, a Centre of Excellence in 2000-2005, first Scientific Director of Biocenter Finland (newly-founded umbrella organisation of the 5 Finnish bioinstitutes) 2006-. Post-doctoral training at University of Medicine and Dentistry, Rutgers Medical School, Piscataway, New Jersey, USA 1982-1985. 150 peer review publications in extracellular matrix biology including first cloning of the key enzyme of collagen synthesis, prolyl 4-hydroxylase and identification of its beta subunit as identical to protein disulphide isomerase, discovery of several collagens, and generation of a patented method for recombinant production of collagens. Supervisor for 26 PhD theses. Member of the Research Council for Health in the Academy of Finland 1998-2003, Member of the Board of Directors for the Center for Scientific Computing 1998- and Vice Chairman 2005-, Member of the Board of the Finnish Cancer Research Organization 2000-, Member of the Ministry of Education Working Groups Biotechnology 2000 and 2005, Chairperson of the Scientific Advisory Board of the Finnish Genome Center 2003-, Member of the Science and Technology Council of Finland 2005-, Member of ESFRI Working Group on Research Infrastructures for Biological and Medical Sciences 2004-

The Anders Jahre´s Nordic Medical Prize for Young Scientists 1994, Member of the Finnish Academy of Sciences and Letters 1995-, The Order of the White Rose in Finland, Knighthood 1st Class 1998, The Science Prize of the State of Finland (shared) 1999.

Prof. Dimitrios Thanos, Director of the Institute of Molecular Biology, Genetics and Biotechnology, Foundation for Biomedical Research of the Academy of Athens, Greece

Prof. Dimitrios Thanos is Director of the Institute of Molecular Biology, Genetics and Biotechnology and Adjunct Professor, Department of Biochemistry and Molecular Biophysics, Columbia University. Prof. Thanos received his Ph.D from University of Crete and was a postdoctoral fellow at Harvard University in the laboratory of tom Maniatis. In 1995 became Assistant professor at Columbia University, Department of Biochemistry and Molecular Biophysics. He was promoter to Associate professor with tenure in 2000. In 2001 he became Director of the Institute of Molecular Biology and Genetics at BSRC "Al. Fleming" in Greece. From March 2006 he is the Vice Chairman of the Scientific Board and Director of the Institute of Molecular Biology, Genetics and Biotechnology of the Foundation for Biomedical Research of the Academy of Athens. He is a Scholar of the Pew Foundation for Biomedical Sciences, Leukemia and Lymphoma Society of America, March of Dimes, Hirschl Foundation and Lucille Markey. has been awarded the Pew Scholars Award in Biomedical Sciences 1996-2000. In 2004 he was elected Member of the European Molecular Biology Organization (EMBO).

Notable publications include:

Lomvardas, S., and **Thanos, D.** (2002). Modifying gene expression programs by altering core promoter chromatin architecture. **Cell 110, 261-271**

Agalioti, T., Chen, G., and **Thanos, D.** (2002). Deciphering the transcriptional histone acetylation code for a human gene. **Cell 111, 381-392**

Agelopoulos, M., and **Thanos, D.** (2006). Epigenetic determination of a cell-specific gene expression program by ATF-2 and the histone variant macroH2A. **EMBO J. (in press)**

- Expert Group on Clinical and Translational Research (EGCT)

Professor Anita Aperia, Professor of Pediatrics at Karolinska Institutet. Astrid Lindgren Children's Hospital, Stockholm, Sweden

Anita Aperia is Professor of Pediatrics at Karolinska Institutet. She chaired the Department of Pediatrics at Karolinska Institutet between 1987-2003. During this time she initiated and planned the building of a new children's hospital, Astrid Lindgren. This hospital includes an experimental research laboratory, where approximately 100 full-time scientists are working. Anita Aperia's group includes 20 members. Her main research interest concerns regulation of salt and water metabolism. She has published a series of seminal papers on the regulation of sodium balance in newborn babies that have had a great impact on the handling of sick infants. She has in experimental studies explored the molecular mechanisms that govern the regulation of salt metabolism. She discovered the role of dopamine for regulation of sodium transport in the kidney. More recently, she has described the regulation of functional dopamine receptors in the brain and identified a new role for the salt pump (Na,K-ATPase) as a signal transducer. Anita Aperia has received numerous awards, including Hamberger Award, Söderberg Prize in Medicine. She is a member of the Royal Swedish Academy of Sciences, where she is presently chairing the Class of Medicine. She has been a member of the Nobel Committee for Physiology or Medicine and chaired the Nobel Assembly in 2001.

Professor Christian Ohmann, Head of the Coordination Centre for Clinical Trials at the Heinrich-Heine-University Düsseldorf, Germany

C. Ohmann has been graduated in mathematics (PhD). Habilitation (1987) and professorship (1993) were acquired in the field of Theoretical Surgery (Surgical Research). Since 1999 C. Ohmann is head of the Coordination Centre for Clinical Trials at the Heinrich-Heine-University Düsseldorf, Germany. His expertise and experience is mainly related to clinical research, medical decision making and clinical trials. In the field of clinical trials there is a focus on IT- and data management and on European

cooperation in multinational trial networks. C. Ohmann achieved the "Richard Merten" award for quality assurance (1995). He is chairman of the working group "Therapeutic research" of the German society for Medical Informatics, Biostatistics and Epidemiology (GMDS), member of the board of the non-profit association "Telematikplattform e.V." and chairman of the Scientific board on health technology assessment at the German Institute for Medical Documentation and Information (DIMDI).

Dr Dimitrios Boumpas, Chairman of the European League against Rheumatism (EULAR)

Dr Boumpas graduated from the Medical School of the University of Ioannina in 1983. Subsequently he received a fellowship from the Fogarty International Center to work as a post-doctoral fellow in Molecular Immunology at the National Institutes of Health (1983-1985). During the next 5 years (1985-1990), he did his residency in Internal Medicine at VAMC/George Town University Medical Center, Washington DC, followed by a fellowship in Rheumatology at the Arthritis Branch, NIH. From 1990-1999 he worked as an Investigator at the NIAMS/NIH where he pursued studies on the pathogenesis and treatment of systemic lupus erythematosus (SLE). While at NIH he served as member of the NIH Clinical Center Committee on Clinical / Translational Research, the NIDDK/NIAMS Institutional Review Board (IRB) and as Clinical Director of NIAMS.

He repatriated in Greece in 1999 as the Director of the Department of Rheumatology, Clinical Immunology and Allergy, and Internal Medicine of the University of Crete. Dr Boumpas is also the Director of the Graduate Program in Clinical Investigation of the University of Crete. From 2001-2002 he served as a member of the Board of Directors of the Hellenic Organization for Medicines. Dr Boumpas is the Chairman of the European League against Rheumatism (EULAR) Task Force on SLE and has served on the Scientific Committees of the EULAR and the American College of Rheumatology (ACR) Annual Meeting. He is a member of the Editorial Board of Annals of Rheumatic Diseases, Clinical & Experiment Rheumatology and Lupus. He has authored over 160 original articles, reviews and chapters in books on the pathogenesis and treatment of human autoimmunity.

Professor Silvio Aime, Professor of General and Inorganic Chemistry and Head of the Center of Molecular Imaging at the University of Torino, Italy

Silvio Aime is Professor of General and Inorganic Chemistry (Degree Course: Biotechnology) and is head of the Center of Molecular Imaging at the University of Torino. Awards: Nasini Medal from the Italian Chemical Society (1987), Medal from the Italian NMR Discussion Group (1996), NMR-Sapio Prize(2000), European Magnetic Resonance Foundation Award (2004). Member of the SMI Council. In the 6th EU-FP Program he is Coordinator of Torino Technologycal & Training Platforms in the two EU Network of Excellence in the field of Molecular Imaging (EMIL and DiMI) and of the STREP Project "Ortho and Para Water" (NEST/ADVENTURE). Industrial collaborations: Bracco Imaging, Serono and KAO (Japan). Coordinator of the National Project on "Innovative Magnetic Resonance Metodologies in Tumoral and Cardiovascular Pathologies".

He is/has been member of the Editorial Board of several Journals and is Editor in-chief of the new journal "Contrast Media and Molecular Imaging" (Wiley). He is author of ca.400 peer-reviewed papers and several patents. His main research activities deal with the development of Imaging Probes for Molecular Imaging applications with MRI modality. Other current research interests are in the field of the chemical characterization of melanin pigments and of Hyperpolarized Para-Hydrogen containing Molecules.

Professor Herbert M. Pinedo, Director of the VUmc Cancer Center Amsterdam, The Netherlands

H.M. (Bob) Pinedo's career is a benchmark for original, top quality, translational cancer research in which he has consistently combined leading-edge basic science with clinical excellence. He is noted as a clinical investigator who takes new concepts to early clinical trials. He has received many awards, including the *Steiner* (1995), *Spinoza Award* (1997) and *Cino del Duca* (1999). He has made seminal observations in cancer biology and treatment-related mechanisms of drug action and

resistance in the patient. Examples of this scientific approach are many of which the following illustrations: the first phase 1 study on daily cisplatin as a radio-enhancer; poor penetration of cytotoxic agents from tumor capillary to cancer cell and lack of relevance of PgP for clinical drug resistance (*NEJM*); discovery that platelets transport VEGF in man (major implications for medical sciences) and their tumor-enhancing role (*Lancet*); close association between (anti-) angiogenesis and coagulation; mobilization of dendritic cells from bone marrow to tumor draining lymph nodes by GM-CSF; and successful use of autologous tumor cells as a vaccine in colon cancer (*Lancet*). His corpus of work is arguably one of the finest examples that well designed translational studies yield paramount discoveries in clinical oncology.

From January 2005 Bob Pinedo has been Director of the newly established VUmc Cancer Center Amsterdam, after being head of the Department of Medical Oncology for 24 years, while as a part-time member of the Department of Medical Oncology he remains active.

Professor Eero Vuorio, Chancellor of the University of Turku, Finland

Eero Vuorio received his M.D. in 1974 and his Ph.D. in 1978, both at the University of Turku. He got his postdoctoral training at the University of Chicago in 1979-1980 and then established his own research group in Turku. He has worked as a visiting professor at the Swiss Federal Technical High School (ETH) in Zürich, and at the M.D. Andersson Cancer Center, University of Texas in Houston. As Professor of Molecular Biology his research focuses on molecular biology of connective tissue, including generation of transgenic animal models for skeletal diseases. In his alma mater, professor Vuorio has served as Vice Dean of the Medical Faculty in 1993-1996, Chairman of the Scientific Advisory Board of BioCity-Turku in 1991-97, Vice Rector in 2003, and as Chancellor of the University of Turku since September 2003. Professor Vuorio has served as the chair of the Medical Research Council in the Academy of Finland in 1998-2003, and as a national representative on several European fora, including European Commission (e.g. Advisory Group to Framework Programme 6, Priority 1, and Forum of Research Managers on Genomics, COGENE), COST Technical Committees on Medicine and Health, European Science Foundation (EMRC and EURESCO), and European Molecular Biology Conference (EMBC). He has served as the chair of the EMBL (European Molecular Biology Laboratory) Council since 2003 and member of the supervisory board of EMBLEM (EMBL Enterprise Management). Professor Christian Ohmann, Head of the Coordination Centre for Clinical Trials at the Heinrich-Heine-University Düsseldorf, Germany

Professor Otmar D. Wiestler, Chairman and Scientific Member of the Management Board of Deutsches Krebsforschungszentrum (German Cancer Research Center, DKFZ), Heidelberg

Otmar D. Wiestler was born in Freiburg, Germany on November 6, 1956. He studied Medicine at the University of Freiburg and received his M.D. in 1984. After training periods at the University of California in San Diego / USA and at the University of Zurich / Switzerland, he was appointed as Professor of Neuropathology and Head of the Department of Neuropathology at the University of Bonn in 1992. At this university, he established a major clinical neuroscience research center. In January 2004 he joined the Deutsches Krebsforschungszentrum (German Cancer Research Center, DKFZ) in Heidelberg as Chairman and Scientific Member of the Management Board. DKFZ represents the largest biomedical research center in Germany. Otmar D. Wiestler has served on many organizational boards, among them as Head of the German Brain Tumor Center in Bonn, Chairman of the BONFOR research committee at the University of Bonn, President of the German Society of Neuropathology and Neuroanatomy, Director of the Neuroscience Technology Platform Life & Brain in Bonn, Head of the Review Board Theoretical Medicine of the Deutsche Forschungsgemeinschaft (DFG), Member and Chairman of the Scientific Advisory Board of Deutsche Krebshilfe (German Cancer Aid). In addition, Otmar D. Wiestler contributed more than 300 papers and book chapters to the scientific literature. Since 2001 he is an elected member of the German Life Science Academy LEOPOLDI

Professor Liselotte Højgaard, Head of Department, Director, Clinical Physiology and Nuclear Medicine & PET and Cyclotron Unit, Rigshospitalet, University of Copenhagen, Denmark

DMSc from Copenhagen University 1991. Head of Department, Director, Clinical Physiology and Nuclear Medicine & PET and Cyclotron Unit, Rigshospitalet, University of Copenhagen, from March 2000. Professor in Medical Technology in Science and Education, Copenhagen University, Faculty of Health Sciences. 130 peer review publications about gastroenterology, physiology, pathophysiology, nuclear medicine and PET. 11 book chapters. Invited speaker at 45 international meetings, with "The Annual Lecture of the British Society of Nuclear Medicine 2005", Key-note speaker European Congress of Radiology, Vienna 2006, European Association of Nuclear Medicine Athens 2006. Supervisor for 10 PhD candidates, evaluator for 15 PhD projects and 5 DMSc candidates. Head of Dept. of Clinical Physiology and Nuclear Medicine & PET and Cyclotron Unit, Rigshospitalet , where we at present have 12PhD students, and 50 peer review publications annually.

Editor-in-chief, Danisk Medical Journal 1996–2002, Member of The Vancouver Group, The International Committee of Medical Journal Editors, 1996-02, Chair 1999-2000, Copenhagen meeting 2000 with new authorship criteria. Editor Nordic Medical Journal, 1995-2000. Circulation 85.000. Courses in leadership, administration and organization, eg. INSEAD, Fointainbleau 2002. Consultant for The European Medicinal Agency 1987-1993. Member of the board of several scientific societies, organizer of symposia and meetings. Member of the board, Vice-president and President, The Royal Medical Society of Copenhagen, founded 1772, 1990-2002. Member of The Danish Council for Research Policy from 2004. Member of AFI, Working Group for Research Infrastructure in Denmark. The Niels A. Lassen Prize 2005.

- Biodiversity and the Environment Expert Group (BEEG)

Professor Pieter Baas, Emeritus Professor of Systematic Botany at Leiden University, The Netherlands

Pieter Baas (1944) is Emeritus Professor of Systematic Botany at Leiden University and was until 2005 the Director of the National Herbarium of the Netherlands and of the National Research School Biodiversity, uniting all research groups and institutes for biosystematics and biodiversity in the Netherlands. His own research focuses on comparative wood anatomy, analysing the evolutionary, ecological, biomechanical, physiological and phylogenetic significance of the stunning diversity patterns in microscopic wood structure of trees, shrubs and lianas. As a director of the National Herbarium of the Netherlands he was a focal point of the Global Taxonomy Initiative of the CBD for the Netherlands and an active member of the Consortium of European Taxonomic Facilities (CETAF) that successfully initiated major EU programmes such as ENBI, Synthesys and EDIT. The National Herbarium of the Netherlands curates a collection of six million dried plant specimens, that are crucial for taxonomic studies and conservation of the flora's of North Western Europe, SE Asia (the Malesian region in particular), Tropical West Africa, and the Guianas in the Neotropics. Open access to these collections was increasingly achieved through innovative digitization projects during his directorship. Throughout his career he has emphasized the European obligations of supporting research on tropical biodiversity and training taxonomists from developing countries.

Professor Birgitta Bremer, Director of the Bergius Foundation and the Bergius Botanical Garden, at the Royal Swedish Academy of Sciences (KVA) and Stockholm University (SU)

Professor Bergianus and director of the Bergius Foundation and the Bergius Botanical Garden, at the Royal Swedish Academy of Sciences (KVA) and Stockholm University (SU). Earlier professor in Plant Molecular Systematics, Uppsala University. PhD in Botany, SU, Post doc at the Missouri Botanical Garden. - Received the Linnaeus prize in botany 2001 from the Royal Physiographic Society in Lund. 1990 my research project was evaluated to be the outstanding systematic project in the Swedish

Natural Science Research Council (NFR) international evaluation. - Supervised six PhD theses and seven post docs. - Published about 100 articles about biodiversity, plant systematics, phylogeny, and molecular phylogenetics. – Selected commissions: board member of GBIF-Sweden (2005-), board member of Uppsala University (2000-2003), chairwoman of the Equal Opportunity Committee for UU (1996-1999), chairwoman of the Swedish Committee for Biology (KVA, 2002-2005), member of the Biology Committee at the research council (NFR 1995-2000), board member of the Willi Hennig Society (1999-2002).

Professor Martin Gerzabek, Professor and Vice-President for Research of the University for Natural Resources and Applied Life Sciences, Vienna

Martin H. Gerzabek was born 1961 in Vienna, he studied agriculture at the University of Agricultural Sciences Vienna; 1993 habilitation (Asc. Prof.) for soil science at the University of Natural Resources and Applied Life Sciences Vienna; 2001 full professor for environmental toxicology and isotopic methods at the same university. Professional career: 1984 scientific staff member of the Austrian Research Centers at Seibersdorf, Institut for Agriculture; 1997 –2003 head of the department of environmental research; since 2001 professor and since 2003 vice-president for research of the University for Natural Resources and Applied Life Sciences Vienna. Fields of expertise: radioecology, especially the investigation of the mobility of radionuclides in the soil-plant system, soil science: soil organic matter dynamics, behaviour of heavy metals and organic contaminants, lysimetry; use of isotopic methods and computational chemistry. President of the Austrian Soil Science Society (2000-2006); Vice-Chairman of the Commission Soil Chemistry of the International Union of Soil Science (2002-2006), Vice-President of the European Confederation of Soil Science Societies (since 2004), Vice-President of the Austrian Association for Management of Contaminated Land (since 2003). 309 scientific publications, thereof 149 peer reviewed journal articles and 23 book chapters; supervision of 5 Masters and 29 PhD theses. Awards: honory member of the Austrian Soil Science Society, Decoration of Honour for Outstanding Contributions to Radiation Protection in Austria in Gold.

Dr Terry Parr, Leader of the Ecosystem Assessment and Forecasting Section at the UK Centre for Ecology and Hydrology (CEH) Lancaster, UK

Terry Parr has been with the UK Centre for Ecology and Hydrology (CEH) since 1978, undertaking research on biodiversity issues related to woodland change, wetland dynamics, vegetation management, climate change impacts and environmental indicators. He is currently Leader the Ecosystem Assessment and Forecasting Section at CEH Lancaster and was Acting Director at CEH Merlewood form 2003-04. From 1990 to 1993 he was seconded to the Department of the Environment (now Defra) where he provided scientific advice to policy and managed a range of research projects including 'Countryside Survey 1990'. Since 1995 he has been the Co-ordinator of the UK Environmental Change Network. His main areas of research are on the detection of climate change impacts on ecosystems and indicators of environmental change. He is involved in the development of the International Networks for Long-term Ecological Research, is co-ordinator of an EC FP6 Network of Excellence to create a "Long-term Biodiversity and Ecosystem Research Network" (ALTER-Net) and is leader of the CEH Programme Theme on "Detection and Attribution of Change in UK and European Ecosystems".

Professor Mario Tredici, Professor of Microbiology at the Faculty of Agriculture of the University of Florence, Italy

Mario Tredici is full Professor of Microbiology at the Faculty of Agriculture of the University of Florence (Italy), where he directs a group working on the mass cultivation and applications of microalgae and cyanobacteria. He has been recipient of research grants from the European Community, the Italian Ministry of Education and Research, the Consiglio Nazionale delle Ricerche of Italy, the Tuscany Region and numerous public and private companies. He currently collaborates with Italian energy companies (ENEL, Enitecnologie) on the use of microalgae cultures for biofixation of CO_2. He has collaborated with renewable energy advisory bodies, including the International Energy Agency (on Task 10 "Photoproduction of Hydrogen") and the Hawaii Natural Energy Institute (on "Sustainable

Bioreactor Systems for Hydrogen Production"), and has co-ordinated a project in collaboration with the CSIRO (Australia) on "Microalgae and microorganisms that are of potential strategic, tactical or commercial interest to both parties". He is currently technical advisor of the "International Network on Biofixation of CO_2 and Greenhouse Gas Abatement with Microalgae". He founded the "Centro di Biotecnologie Fotosintetiche" and Fotosintetica & Microbiologica S.r.l., a spin-off company of the University of Florence. He was among the founders, and its President from 2002 to 2005, of the International Society for Applied Phycology (ISAP).

Dr Fanny Voutsinou-Taliadouri, Research Director in the Hellenic Centre for Marine Research, Greece

Dr. F. Voutsinou-Taliadouri (B.Sc. in Chemistry, Ph.D. in Geochemistry) is Research Director in the Hellenic Centre for Marine Research. Over 33-year experience in Oceanographic, Environmental studies (Geochemistry of modern sediments and their environmental impact; Heavy metals in biota, sediments and seawater; Biogeochemistry). Responsible in EU/International Projects: UNEP MED-POL, MAST-0015-C(TT), MAST-II PELAGOS, MAST-III MATER, INTERPOL. Coordinator or partner in more than 50 Research Projects funded by National and International Organizations. Member of Scientific, Steering, Advisory and Evaluation Committees. President of Organizing Committees for International Meetings. Member of Editorial Board of Scientific Journals. Member of Scientific National and International Associations. Referee in International Journals. National Representative in numerous International Expert meetings. National Representative in the EUROMAR Board (1990-..). Member of the Steering Committee and National Coordinator of the QUASIMEME (1990-..). Representative of the Hellenic Delegation in the IOC General Assembly (2003-..). More than 100 publications (more than 350 citations) in International refereed Journals (Anal. Chim. Acta, Mar. Biology, Mar. Geol., Oceanol. Acta, Mar. Poll. Bull., Mikrochim. Acta, Est. Coast. Shelf Sci., Progr. in Ocean., J. of Chromat., etc) in the field of Chemical Oceanography, Marine Biogeochemistry. Evaluator in Community Programmes: BCR (Measuring & Testing 1990, 1992)/ MAST (1991)/ TMR (Earth Sciences 1995, 1997, 1999)/ RTD (Sustainable Marine Ecosystems 1999)/ RTD (Global Change, Climate & Biodiversity 2001) RTN (Geo- & Environment, 1999, 2004, 2005/ New Instruments (IP & NoE Global Change & Ecosystems 2004)/ RTN (Human Resources & Mobility 2005)/ RTN (Life & Environment 2005, 2006)/ Marie Curie Fellowships (2000, 2001, 2004, 2005)/ Marie Curie Fellowships EIF, OIF, IIF 2005, 2006).

Professor Wolfgang Weisser, Professor for Terrestrial Ecology at the Friedrich-Schiller-University of Jena, Germany

Wolfgang W. Weisser is Professor for Terrestrial Ecology at the Friedrich-Schiller-University of Jena, Germany. He studied Biology and Mathematics at the Universities in Gießen and Bayreuth and graduated in 1991. He completed his D.Phil. at the University of Oxford in 1994. After two postdocs at Imperial College at Silwood Park, UK from 1994-1996, and the University of Basel, from 1996-1999 he moved to Jena in 1999. His research focuses on the relationship between biodiversity and ecosystem functioning, He is coordinator of the "Jena experiment" where experimental grassland ecosystems are created that range from one to 60 plant species and where a number of research groups study the effects of diversity on ecosystem functions such as trophic interactions, productivity, carbon storage and element cycles. He also coordinates studies on the relationship between land use, biodiversity and ecosystem functioning in agriculturally influenced landscapes. His personal interest is in the role of insects for ecosystem functioning.

Professor Mari Walls, Director of the Center for Environmental Research, University of Turku, Finland

Mari Walls received her Ph.D. in Zoology in 1989 at University of Turku. She got her postdoctoral training at Cornell University and University of Washington, USA in 1990-1992 and then established her own research group at the University of Turku. Her research has been focussing on life history ecology, ecological interactions, aquatic ecology, biodiversity and natural resource management. She received her docentship in Ecology at the University of Helsinki in 1995. She has been working as

Professor in Biodiversity and Environmental Research at the Department of Biology, University of Turku and Head of the University of Turku Ruissalo Botanical Garden and the Zoological Museum and the Herbarium in 2000 and 2004-2005, Director of the Center for Environmental Research, University of Turku, and Programme Director of the Finnish Biodiversity Research Programme FIBRE, University of Turku in 1997-2003 and Research Director of the Maj and Tor Nessling Foundation in 1995-1997. Start ing January 2006, she has been appointed as Director of Environmental Research, MTT Agrifood Research Finland. Dr. Walls has served as an expert and national representative on several European and international fora, including the Expert Advisory Group on Global Change, Climate and Biodiversity/ EC FP5 in 1998-2000 and 2000-2002, the ESF EUROCORES Project on Biodiversity (EuroDIVERSITY) in 2004, the OECD Task Force on Biological Resource Centers in 1999-2005, OECD MegaScience Forum on Global Biodiversity Information Facility GBIF initiative in 1999, and the SCAR Foresight Expert Group on agriculture and agricultural research in Europe in 2006.