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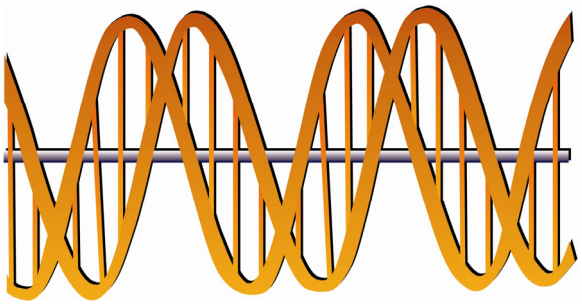

# Biological and Medical Sciences

# Roadmap Working Group Report 2008

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# PREFACE

It is now universally understood that all domains of science and technology require appropriate infrastructures. These are of different nature for each domain. Instrumentation in the Life Sciences is very important albeit rarely unique: usually it consists of instruments or combinations that can be acquired at several locations, mixed and matched into infrastructure systems and used or updated as needed. EMBL, Europe's paradigm of an integrated Life Science Infrastructure, has contributed substantially with the development of instruments and methods e.g. in Bioinformatics and Structural Biology as well as the training and broad access that it offers to the community for continuously evolving facilities. These will be complemented with the new Life Sciences Infrastructures that are being initiated across Europe under the ESFRI process. The European Life Sciences can look forward to acquiring the robust collection of infrastructures which are now essential for cutting-edge biological research.

Instrumentation for modern Molecular Biology in Europe and beyond typically consists of many compact instruments for synthesis and sequence analysis of macromolecules, for imaging of biological structures and materials at various levels of resolution, or for Bioinformatics, Chemical and Systems Biology. Dedicated facilities and instrumentation will be crucial for "biobanking" biological materials such as tissue samples, microbial strains and whole model organisms, and chemicals that can be used to control specific biological processes.

This brief summary of Life Sciences infrastructures is not exhaustive – it is meant to convey their immense importance and variety. In the coming years, the competitiveness of Europe in Science, "the endless frontier" will depend on the availability of outstanding investigators, appropriate conditions like sustainable funding and legal structures, as well as excellent facilities.

We will need an ambitious combination of ERC, ESFRI and research-intensive institutions, both national and international.

Fotis C. Kafatos

Scientific advisor to the BMS RWG

European Research Council President and Chairman of its Scientific Council

# FOREWORD

ESFRI Forum asked the Biological and Medical Sciences Roadmap Working Group (BMS RWG) at its meeting in June 2007 to prepare a report for the update of the ESFRI Roadmap in 2008 covering three areas:

- a scientific landscape of the Life Sciences in Europe,
- a report on the six Life Science Research Infrastructures (RIs) which were on the first edition of the Roadmap and are presently in the preparatory phase
- recommendations for new or upgraded Pan-European RIs.

As in its first edition of the Roadmap, ESFRI expected new proposals for RIs for the next 10 – 20 years to improve Europe's research competitiveness for reaching the Lisbon targets. The RI proposals in this report are mostly distributed facilities and are often different in kind to RIs in other fields of science.

BMS RWG received various scientifically outstanding proposals addressing very important areas in Life Sciences. Four proposals for RIs showed the character of a RI as opposed to a research project as well as the pan-European nature rather than a mere regional or national RI. Developing a comprehensive roadmap is a work-in-progress which requires the continuation of the BMS RWG as well as further updates to complete.

BMS RWG members are happy to report on the progress the six Life Science initiatives which were included in the first edition of the Roadmap in 2006. They all applied successfully for the Preparatory Phase, which is funded by the European Commission and reached very high scores. The Kick-Off meetings in each case showed a very great promise.

All 29 members of the BMS RWG would have welcomed more time for their deliberations particularly for the scientific evaluation. Instead of following the 'lessons learned' from the preparation of the first Roadmap and giving more time to the RWGs, the update process took place under an even greater time pressure than before. BMS RWG presents some recommendations for the future ESFRI process at the end of its report.

The Chair wishes to thank all the experts who worked in complimentary with the four Expert Groups. Moreover, the work of BMS RWG would not have been possible without the spirit and the dedication of all members of BMS RWG coming from 29 different Member States. Everybody worked hard to bring Life Sciences to the forefront of European Research. The Chair also wishes to express his appreciation to the BMS Secretariat, Dr. Stefanie Zeretzke, Jan Skriwanek and Marie-Christine Mahlke, who made this report reality. A special thank of the BMS RWG is addressed to the German Federal Ministry for Education and Research, who funded the BMS Secretariat.

The BMS RWG recommends four new RIs to the ESFRI Forum for the inclusion into the update of the Roadmap 2008. All of them address the clear needs of the European Life Sciences for improved and more sustainable RIs and its funding, to enable European researchers to participate in the world league of life science research. The ESFRI process has already proven of considerable benefit to the Life Sciences and the new additions to the Roadmap will extend and strengthen competitiveness and productivity to more fields and promise further benefit to society and the economy. The BMS RWG hopes that the present report helps the life science research in Europe to reach the importance it deserves for the benefit of mankind.

Eckhart Curtius

Chair BMS RWG

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# 1 EXECUTIVE SUMMARY

Research infrastructures (RIs) are the most powerful means to foster cooperation on a pan-European scale and to provide efficient access to advanced methods and technologies for the scientific community.

The existence, availability and easy access to leading research infrastructures is a key determinant of EU competitiveness in basic and applied research, offering a major opportunity for discussions, ideas, interchange and major collaborations within the field of biological and medical sciences.

The main objective of the BMS RWG was to promote the development of a landscape of RIs within the biological and medical sciences. In fulfilling this task BMS RWG first defined the range of its consideration in the Life Sciences and the respective scientific areas of importance for life science research in Europe. On the basis of this scope the BMS RWG created a landscape of RIs in the Life Sciences, incorporating the RIs already on the Roadmap (RM), RIs which are suggested to be taken onboard in the 2008 update and future RI needs that are still to be addressed (see chapter 2).

To do this, the BMS RWG had to evaluate and identify potential new major pan-European RIs or major upgrades of existing RIs in context with existing preparatory phase (pp) ESFRI RM RIs. Furthermore BMS RWG monitored through regular meetings, the progress of the pp RIs.

The BMS RWG met six times to address the update of the RM. The main task was the preparation of the BMS report, reporting on the RIs already on the RM and on the future RIs to be included into the update of the ESFRI RM.

A meeting of the Coordinators of the pp RIs, to exchange experiences, strengthen their cooperation and to provide advice from BMS RWG members to the coordinators took place in Brussels in June 2008. Scientific officers from the EC services also gave BMS RWG regular oral reports on the progress in the negotiations of pp RI contracts. Based on these reviews and the information provided by the coordinators of the pp RIs, the BMS RWG concluded that all 6 were developing in a very effective manner and consequently they deserve inclusion in the ESFRI RM 2008 (see Table 1 and chapter 3).

| No. | Title | Progress/Events | Status | |
|---|---|---|---|---|
| | | | PP Start | Funding Partners |
| 01 | BBMRI | ▪ 17 March 2007: Partner and Stakeholder Meeting<br>▪ 10-12 February 2008: Kick-Off Meeting<br>▪ 17-18 April 2008: Joint Meeting of Participants and Associated Organisations<br>▪ 18 April 2008: Governance Council Meeting and Scientific and Ethical Advisory Board Meeting<br>▪ 28 May 2008: Seminar at the European Parliament | Feb 2008 | 21 |
| 02 | EATRIS | ▪ September 2007: Project Partner Meeting<br>▪ 25 March 2008: Kick-Off Meeting | Jan 2008 | 7 |
| 03 | ECRIN-PPI | ▪ 27 February 2008: Pre-Kick-Off Meeting<br>▪ 20 May 2008: Kick-Off Meeting | March 2008 | 6 |

Table 1: Overview on the progress of the 6 BMS RIs in pp

| No. | Title | Progress/Events | Status | |
|---|---|---|---|---|
| | | | PP Start | Funding Partners |
| 04 | ELIXIR | ▪ 28-29 January 2008: 1st Steering Committee Meeting<br>▪ 9 April 2008: 2nd Steering Committee Meeting<br>▪ 10 April 2008: 1st Stakeholders Meeting<br>▪ 29 October 2008: 3rd Steering Committee Meeting<br>▪ 18 November 2008: 2nd Stakeholders Meeting | Nov 2007 | 16 |
| 05 | INFRAFRONTIER | ▪ 2-3 June 2008: Kick-Off Meeting<br>▪ 30 July 2008: Strategy Meeting | March 2008 | 12 |
| 06 | INSTRUCT | ▪ 23 March 2008: Management Committee Meeting<br>▪ 5 May 2008: Kick-Off Meeting<br>▪ 16 October 2008: Stakeholders Meeting<br>▪ May 2009: Annual Meeting<br>▪ May 2010: Annual Meeting | April 2008 | 5 |

Table 1 (continued): Overview on the progress of the 6 BMS RIs in pp

To ensure a high quality evaluation of the new proposals, the BMS RWG established four Expert Groups. These reviewed the needs of the potential user communities within the next 10 to 20 years. They assessed and identified RIs according to the ESFRI stage gate process, taking into account the strength of the scientific case and the extent to which the proposed RI was technologically and financially feasible. In addition, the Expert Groups considered the possibility of open access for the user, the mechanisms for other partners to join later, to ensure the continuous upgrade of the RI in an open and effective way. The Expert Groups recommended 4 proposals as mature for inclusion in the first Update of the ESFRI RM and one emerging proposal that requires more analysis and elaboration (see Table 2).

| No. | Title | Other RWGs involved | Recommendation | | Scope |
|---|---|---|---|---|---|
| | | | Roadmap | Emerging | |
| RU01 | BLS4 | | X | | X |
| RU02 | EISB | | | X | X |
| RU04 | EU-OPENSCREEN | | X | | X |
| RU05 | EurIMon | | | | X |
| RU16 / 41 | Euro-BioImaging | | X | | X |
| RU17 | CECAM | eIWG+BMS, ENV, PSE, SSH | | | |
| RU18 | EUSHAPE | | | | X |
| RU22 | EMBRC | BMS+ENV, eIWG | X | | X |
| RU23 | EURAT | ENV+BMS | | | |
| RU25 | FASOF | ENV+BMS | | | |
| RU30 | ASSA | ENV+eIWG | | | X |
| RU31 | Software Service | eIWG+BMS, ENV, PSE, SSH | | | |
| RU32 | ANAEE | ENV+BMS | | | |
| RU33 | IPURE | eIWG+BMS, ENV, PSE, SSH | | | |

Table 2: New proposals for RI

The first report of the BMS RWG (2006) mainly focussed on the area of biomedicine.

Following a request from ESFRI Forum BMS RWG widened its scope in the beginning of

2007 to two additional areas covering both the fields of resources and production systems and the basic biological sciences. In its report 2008 BMS RWG suggests 4 RIs, to fill the gaps which still seem to exist (see Chapter 4):

One of the basic needs in Life Sciences, essential for all its fields from basic biology such as cellular or developmental biology to applied science in medicine and industrial biotech is the development of access to novel **Imaging Technologies.**

A great opportunity for the scientific community as well as for industry is the research area of **Chemical Biology**, which deals with studying probe systems *in vitro* and *in vivo* with low molecular weight compounds (small molecules). This approach offers the possibility to systematically screen, on a large scale basis, for new bioactive agents of application in a wide range of areas from human and veterinary medicine, to agriculture and nutrition.
The increase in emerging and re-emerging infectious diseases involving highly pathogenic micro-organisms means that there is a real need for Europe to build up its RI of **High security laboratories** to address potential threats such as SARS and H5N1.

The demand for marine organisms used as models to investigate fundamental questions in biology is constantly increasing. The **marine biological stations** provide access to these organisms. The results from experimental work in biomedicine, biochemistry, physiology and systematics can be used further in areas like aquaculture and those developing new materials, e.g. medicines and bio-fuels.

# 2 UPDATE OF THE SCIENTIFIC LANDSCAPE

## 2.1 European RIs in the BMS field

The understanding of the complexity of form, function and interaction of organisms, embodies the challenges of the present day biology. Life Sciences are now well poised to find answers to complex fundamental scientific questions by utilizing the huge amount of data produced from high-throughput approaches, and by applying this data for the improvement of health, agriculture, environment and society at large. To rise to the challenge and reach these goals it is necessary to break new ground and to greatly increase interdisciplinary work. Scientists from very different fields, from physicians to engineers, from biologists to environmentalists, need to share their knowledge as well as their ways of thinking in order to solve the present or future problems to which our society is or will be exposed.

The critical analysis of the BMS landscape, considering the different scientific areas and methodologies, of which it is formed, will help to better integrate and manage these tasks in the future.

### 2.1.1 History of European RIs in the BMS field

In the field of BMS RIs are typically located in direct association with the user community, and RIs, even international ones, are usually of a distributed nature. The prime example of a European distributed RI in the area of BMS is the European Molecular Biology Laboratory (EMBL). This is Europe's flagship laboratory for basic research in Molecular Biology and is supported by public funding from 20 member states and one associate member. The EMBL was started up in 1974 and consists of a main centre Laboratory in Heidelberg, and four Outstations in Hinxton (the European Bioinformatics Institute-EBI), Grenoble, Hamburg, and Monterotondo near Rome. Research at EMBL is currently conducted by approximately 85 independent groups covering the spectrum of Molecular Biology, including Cellular Biology, Structural Biology and Bioinformatics. EMBL has a five-fold mission: to carry out excellent basic research in Molecular Biology, to provide services to the scientific community, to train young scientists , to develop new technology and instrumentation and to make technology available to the society at large. Rather than relying on one large single-site entity, EMBL has succeeded by

- carefully selecting and hiring the best young research group leaders and giving them early independence and sufficient funding to pursue their own discoveries and ideas;
- bringing together a new youthful, multidisciplinary, and international scientific community, capable of pushing forward new fields;
- adopting and combining technologies as they arise;
- providing training in these technologies internally as well as to a large number of visitors and participants in workshops and courses, often co-sponsored by EMBO;
- giving mostly fixed-term rather than permanent appointments to its staff, thereby promoting moving-on to new positions and the dissemination of scientific approaches and technologies in Europe;
- most recently, establishing several locally funded partnerships with carefully selected institutions in member states which wish to invest in bringing the EMBL model to their national research organisations.

The success of EMBL is not only underpinned by the distributed character. This RI fulfils all requirements needed for biological research, through close cooperation with other scientists outside the biology field. The activities at EMBL Hamburg, for example, focus on state-of-the art Structural Biology methods using synchrotron radiation, which is situated on the campus of the German Synchrotron Research Centre (DESY). This cooperation is based on a suggestion made by Ken Holmes to Sir John Kendrew, the first Director General of the EMBL. Initially, EMBO gave modest funds to pursue experiments at DESY, and an Outstation at Hamburg was added to the EMBL proposal, along with another Outstation in Grenoble, where EMBL would coordinate the biologi-

cal uses of the neutron beams produced by Institute Laue-Langevin (ILL) and the X-ray diffraction capabilities of the adjacent ESRF synchrotron. Nowadays the research at EMBL Hamburg and Grenoble is tightly associated with the available synchrotron experiment stations for applications in Life Sciences. Several projects aim to develop novel technologies to advance methods in Structural Biology through automation and greater user friendliness.

Similar infrastructures have been established and widely used at Daresbury (UK), LURE (France), Elettra (Italy), BESSY-II (Germany), MAX II (Sweden), Diamond (UK), SLS (Switzerland), Soleil (France), and are currently under construction at PETRA III at DESY (Germany) and ALBA (Spain).

Moreover, EMBL has developed into a successfully working distributed RI on a global level. The Nucleotide Sequence Database (which was established at EMBL Heidelberg in 1980 and is today located at the EBI) is an international collaboration between the EMBL Nucleotide Sequence Database (Europe), GenBank (USA) and the DNA Database of Japan (Japan). It is part of the tri-partite International Nucleotide Sequence Database Collaboration DDBJ/EMBL/GenBank, managing sequence data worldwide since 1982. Historically it was tightly coupled to the publication of sequences in the scientific literature, but electronic submission rapidly became the usual practice. Today, the volume of data submitted by direct transfer of data from major sequencing centres, such as the Wellcome Trust Sanger Institute, overshadows all other input. In recent years the EMBL database has doubled in size almost yearly, and currently contains about 110 million sequences and 200 billion base pairs. New DNA sequencing technology is now making projects such as the 1000 genomes possible leading to an even higher increase in the amount of data. The EMBL-EBI website, the main portal for users of biological information in Europe, receives over 3 million hits per day.

Another example for a successful cooperation demonstrating the nature of Life Sciences and thereby explaining the usual nature of distributed RIs is the Human Genome Project (HGP), which was a 13-year project coordinated by the U.S. Department of Energy and the National Institutes of Health. During the early years of the HGP, the Wellcome Trust (U.K.) became a major partner; additional contributions came from Japan, France, Germany, China, and others. Taken together hundreds of laboratories world-wide have been involved in this project.

### 2.1.2 Novel concepts for European RIs

At the start of the ESFRI process RIs were defined as facilities, resources or services that are needed by the scientific community for development of leading-edge research, as well as for transmission, exchanges and preservation of knowledge in their respective field. These include singular large-scale research installations, collections, special habitats, libraries, databases, biological archives, clean rooms, integrated arrays of small research, installations, high-capacity/high speed communication networks, research vessels, satellite and aircraft observation facilities, coastal observatories, telescopes, synchrotrons and accelerators, networks of computing facilities, as well as infrastructural centres of competence which provide a service for the wider research community based on an assembly of techniques and know-how. RIs may be 'single-sited' (a single resource at a single location), 'distributed' (a network of distributed resources), or 'virtual' (the service is provided electronically).

A RI needed to support biological and medical sciences can be different to that for the physical or engineering sciences in that it is often distributed (comprised of multi-site facilities) and it may consist of collections of data or materials underpinned by systems for collection, storage and access. The cost involved in providing infrastructure for biological and medical sciences is not so much in construction as in costs for running, maintaining and continuously developing the facilities. Moreover, the infrastructure for biological and medical sciences may not need to be 'decommissioned' in the way many infrastructures in the physical and engineering sciences require as technology changes: instead they may need to be 'recommissioned' as they expand, take on new functions or are transferred from one responsible operator to another. The distributed nature of most of the RIs for biological and medical sciences means that many different countries and institutions can participate in their establishment or in their development.

### 2.1.3 Increased Relevance of RIs in Life Sciences

Research in Life Sciences has changed markedly during the last few years. Whereas in previous years scientific progress was mainly achieved by individual research groups focussing on very specific aspects (classical reductionist hypothesis-driven research), more holistic approaches (discovery-driven research) that rely on large distributed team, with common access to expensive infrastructure, are becoming increasingly important. Challenges such as obtaining better insight into the role of genes and their products in the context of the complexity of living systems or to understand the genetic and environmental factors impacting on human health requires interdisciplinary approaches involving a broad spectrum of demanding technologies and resources. The current fragmentation of the scientific communities in Europe is a major obstacle to this and single institutions or even national networks are often not able to address this need. This deficiency in the European life science landscape should be overcome by pan-European RIs which will provide the proper framework for collation of resources as well as the access to and integration of high-end technologies and expertise required to address key scientific questions.

The pp RIs are the first step to building up European scale RIs addressing these needs of the scientific community. For instance, the demand for biological information is growing rapidly and the existing structures to collect, deliver and analyse these data are fragmented. ELIXIR is the most promising RI in the area that brings together data from a wide variety of sources and making them accessible to the research community in a user-friendly manner. BBMRI is another example aiming to build up a bio medically relevant, quality assessed sample collections, highly beneficial for the scientific community, especially in the field of clinical research. Nowadays the new trend in the biological and medical sciences is towards the collaboration of scientists from various fields within and outside from the BMS community. Within the BMS community there is a need to promote greater cross fertilisation between sub-disciplines, for example, there needs to be more linkage between plant and biomedical scientists. However, this is probably not the main challenge for scientists in the BMS field. The alteration of thinking, from reductionist to whole systems approaches e.g. from the study of single signal transduction pathways to the simulation of the influence of a special drug in patients, requires integration of many technologies and approaches and the engagement of the involvement of scientists from the physical, engineering and the mathematical sciences together with the conventional life sciences community.

### 2.1.4 Global dimension of the Life Science RIs

Challenges in life science research are increasingly global and, therefore, can only be efficiently addressed by RIs with a global scope. For example, the OECD identified in its report “Underpinning the future of Life Sciences and biotechnology“ that access to biological resources and collections – living organisms, cells, genes, and related information – are the essential raw material for the advancement of biotechnology, human health, and research and development in Life Sciences. OECD proposed a global biological resource centres network (GBRCN). This global dimension is also reflected by BBMRI in that it plans to implement the OECD GBRCN concept for Europe and closely cooperates with leading US and Asian initiatives. Other examples include a global structure for genomic sequence data and archiving of mouse models (Infrafrontier).

The increasing number of global diseases is another reason to develop RIs on a global level. International concern was well exemplified in the case of SARS, an emerging disease. Export of viral or bacterial infections in cattle farming with consequent major economic loss, or the possibility that insect vectors may emerge in newly developed niches where they never existed or from where they were previously eradicated (as in dengue or yellow fever) are also of current concern.

Problems arise when new diseases appear, as much as when old ones re-emerge. Globalization of travel, human and animal mobility has been a benefit to society but it can also be the basis of transfer of pathogens or their vectors into new regions. The economic loss associated with these diseases is immense.
Diseases in old age are a particular problem, we not only one have to offer to the elderly a high level of life quality but also be prepared to reduce the prevalence of ageing associated diseases with good and early diagnosis. Overall improvement in health is related to better

diagnosis of disease, proper treatment (therapy) or control (vaccines or drugs). It is increasingly recognised Human and Animal health are associated.

Good application and exchange of research data, and collaboration with Industry as a relevant partner in the use and application of such data, is essential. Often it takes a good length of time between "discovery" and "application" for reasons that are often unfamiliar to scientists.

The biological and medical and social sciences are distinct though complementary and research has to be problem and action oriented. The establishment of well coordinated infrastructures aims at health in general, for the benefit of humans or animals - both in case of zoonosis. Thus the appropriate mix of researchers, decision or policy makers, practitioners and funding agencies, must be brought to bear on the problem. Today's most pressing environmental problems such as climate change, global warming, and lack of quality in water supplies will affect health in general. This requires stronger cooperation between the ENV and the BMS RWGs. Many environmental changes influence the biological pathways and thereby potentially changing the nature of life.

The establishment of major BMS RIs is vital in strengthening the scientific and economic competitiveness of the European Research Area, and an association with other regions of the globe will enhance this and contribute to global health and prosperity.

#### 2.1.5 Interrelation between the ESFRI- and various national Roadmaps

In contrast to research projects, RIs require large funding for long periods to ensure sustainability and development. Critical for development and implementation of the ESFRI RM is the commitment of the Member States (MS) to fund the RIs. Ideally such commitments should be made during the preparatory phase. User communities gain merit from the international RIs when the national and local infrastructures integrate well with the pan-European ones. The ESFRI process has had a tremendous impact on promoting the planning of national RMs for RIs. This impact is particularly strong in fields, such as Life Sciences, which until now have not had a tradition of joint planning and pooling together resources for large-scale RIs. Several European countries have recently prepared or are in the process of preparing their own RMs, and the ESFRI RM is of high importance for this preparation. The ESFRI RM and the respective national RMs have a positive feedback effect on each other, offering the prospect of a proper and efficient implementation of the RMs through a reliable and increasing level of sustainable financing.

### 2.2 BMS RWG´s scope

In the beginning of 2007 the BMS RWG widened its scope from biological and medical applications to applied and basic biology. The following fields of action have been identified (see Table 3).

The BMS RWG observed the necessity to acknowledge the increasing demand for safer, healthier, higher quality food and for the increased use of renewable bio-resources.

There is an increasing integration of Basic Biological Sciences, with application. Areas such as Developmental Biology increasingly produce results which are used in medical sciences and lead to an improvement of diagnosis and therapies of diseases. One of the most prominent examples is the discovery of the human transcription factor and tumour suppressor p53. Auto-antibodies to this protein are currently used for diagnosis. Facilities and institutes of basic biology often provide biological resources and facilities.

It is more than clear that improvement of health is strongly associated with a number of factors related to the economy (e.g. national development, local or regional economies, poverty and mal-nutrition) and environment (natural disasters or catastrophes).

### 2.3 Identifying the needs for the new generation of the Life Sciences RIs

In general one can identify tools and methodologies on the one hand and fields of research on the other hand, embedded in three distinct pillars of research, i.e.:

- the biological sciences,
- the production and resources systems,
- the medical sciences (compare 2.2)

| Biological Sciences | | Biological Resources and Production Systems | | | Medical Sciences | | |
|---|---|---|---|---|---|---|---|
| Evolution, Development and Diversity of organisms | Anatomy and Physiology of organisms, Behaviour and Ecology; Interaction of organisms | Plants, Animals, Micro-organisms, Bio Energy and Bio Fuels | Sustainability Safety and Quality, Health and Welfare, Infectious Diseases, Zoonoses | Human Nutrition, Aquaculture, Agrifood, Livestock production | Epidemiology | Diagnosis, Prevention, Therapy | Public Health |

Table 3: BMS RWG's Scope

### 2.3.1 Imaging

Together with databases, and biobanks, innovative imaging techniques are the key tools for all scientists from the Life Sciences. Imaging is essential for studying living systems at the molecular, the cellular and the physiological level from single cells through model organisms to humans. Thereby it services all scientific fields from basic cell and developmental biology through to applied science in medicine. The development of advanced light microscopy methods and biomedical imaging has rapidly advanced over the last decade, together with an explosion in the use of digital imaging techniques initially in basic research. The challenge for biomedical imaging is 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. There is an unmet need for non-invasive high resolution imaging techniques without radiation burden which can accurately predict, diagnose and monitor therapeutics and treatment procedures in patients at the organ, tissue, cellular and sub-cellular levels.

Multiphoton live imaging is particularly useful for studying thick sections, e.g. brain slices, skin, vessels, Zebrafish heart. The most challenging problems, e.g. in the field of oncology, cardiovascular and neurological diseases, can be tackled by the implementation of a concerted European effort in biomedical imaging to promote human health care. A RI for non-invasive, real time, 4 dimension imaging at every level from molecule to man (patient) promises real benefits at the European level.

Without imaging techniques like pQCT (peripheral quantitative computed tomography) and µCT (micro computed tomography**)** the analysis of dysmorphologies in mutant mice (Infrafrontier) are not feasible.

Clinical imaging is also becoming relevant to secure investigating of pathophysiological phenomena directly in patients with the development of molecular tracers and multimodality tracers for molecular imaging (SPECT, PET, MRI, optical imaging). The development of ultra high field MRI that simultaneously allows fast morphological analysis (MRI imaging), functional analysis (fMRI) and biochemical analysis (NMR spectrometry) will also contribute to clinical investigations notably in neuroimaging with fMRI in the field of cognitive sciences.

Moreover imaging depends on facilities and expertise in bio-computing and bioinformatics, physics and chemistry. The development of novel labelling and imaging techniques such as non-fluorescence based approaches and detection systems, (e.g. coherent Anti-strokes Raman Spectroscopy and Surface Enhanced Raman Spectroscopy Microscopies) are becoming increasingly relevant for biomedical imaging and as technologies to be provided widely through this RI.

The funding and human expertise required to establish the infrastructure considerably exceeds the financial and the scientific capabili-

ties of an individual laboratory or a single institution, and most individual national research funding bodies. To address the problem of resource fragmentation, the proposed RI should have a distributed character and be interlinked to Integrated Biological Imaging Centres of excellence in most member states, so that all basic science research laboratories will have access to the latest technology and expertise.

In almost all MS there have been efforts to build infrastructures in Imaging. The EU, within its FP 6 in the area "Life Sciences, genomics and biotechnology for health" and in the FP 7 in the area "Health", promoted the development of imaging techniques. So it is obvious that, next to the development of databases and management of data, the development and access to imaging techniques play a pivotal role for the scientific community in the field of BMS.

### 2.3.2 Systems Biology (SB)

SB is a progression from the profound developments that the Life Sciences underwent during the last half of the 20th Century and has the prospect of transferring all fields of the Biological and Medical Sciences. It represents a highly interdisciplinary approach, which is nowadays indispensable to apply the knowledge arising from e.g. genetic research.

At present complete annotated genome sequences are available for man and many model organisms, including our closest relative, the chimpanzee model and crop plants and many beneficial or pathogenic microbes. Comprehensive maps of genome variations and polymorphisms paint a rich picture of our population and evolutionary history and off the means to explain genetic, epigenetic and environmental contributions to life processes. SB integrates bioinformatics and modelling of genomic data in an attempt to predict and explain the functional architecture of genomes across the diversity of organisms. By recognizing that biological systems are far too complex for a completely reductionist analysis SB tightly integrates high through-put experimental approaches in molecular biology, biochemistry and chemistry together with bioinformatics, novel physical/chemical and engineering technologies, and mathematical approaches, including modelling and simulation.

There is certainly an urgent need for SB RI in Europe and there are many initiatives in this field. The European Science Foundation (ESF) published a strategic paper in August 2007 on the importance of Systems Biology as a „Grand Challenge for Europe". It recommended to establishing a task force to define a European RI. Also the formation of an ERA-Net for SB (2006, see report ERASysBio, 11/2007) demonstrates the importance of this topic in strengthening the European Research Area. The EC is funding around 20 projects under FP 6. Many several hundreds of laboratories around Europe are involved, with more than 85 Mio € in EC funding.

A number European States are very active in SB. In Germany the "HepatoSys" initiative is funded by the German Federal Ministry for Education and Research, dealing with the creation of a virtual liver cell. In the UK the BBSRC/EPSRC Centres for Integrative Systems Biology (CISBs, see as well as report of Academy of Medical Science and the Royal Academy of engineering 02/2007) have been formed, and Israel, Switzerland, the Netherlands, Spain, the Scandinavian countries as well as several other member states and the EMBL are also active. What is now needed is a distributed European Infrastructure that would greatly facilitate and support the involvement of highly qualified scientists, across our continent in this new scientific revolution and make the best use of disparate national investments in infrastructure.

SB promises to deliver practical advances in healthcare and industrial biotechnology including the food and environmental sustainability sectors. Beyond molecular and cellular biology, it is able to address highly complex research areas, such as pharmacology, animal and human physiology, tissue regeneration, metabolism, detoxification of xenobiotics and the immune and nervous systems. It is of intense interest to the food and pharmaceutical industries, where SB should facilitate significantly shorter periods for product development and testing. New directions in SB research are opening up opportunities to study interactions of organ systems and even populations in plants and animals, thus promising new advances in medicine, ecological management, the food industry and animal husbandry.

A European SB RI established throughout Europe would be highly interconnected to

promote large scale problem-led scientific collaborations, to promote integration in technology development, to serve as training sites by creating or participating in national and international PhD programmes in SB and to ensure adequate human capacity for this new critical interdisciplinary area.

### 2.3.3 Synthetic Biology

The youngest discipline within the field of Life Sciences is Synthetic Biology. In contrast to genetic engineering, which is based on the alteration of existing genetic information, Synthetic Biology deals with the design and construction of novel functional entities from the assembly of naturally occurring or artificial subcellular components (biobricks), producing designed cells or organisms. Synthetic Biology combines the knowledge from the fields of Molecular Biology, Organic Chemistry, Nanobiotechnology, Information Technology and Engineering.

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 and following on from Systems Biology. Just as all engineering disciplines maintain a fruitful relationship with its fundamental sciences, 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 new 'biological systems' in a rational and systematic way.

In 2005 the European Group of Life Sciences (EGLS) identified 15 scientific challenges that were believed to contribute to tackling the societal problems (e.g. human health and environment), and which could help shape the European research agenda in the coming years. One selected area is Synthetic biology. In US funded by MIT the Synthetic Biology Engineering Research Centre (SynBERC) was established. In Europe the EC funds, in the NEST Pathfinder Initiative, with 20 or so projects covering a wide range of different topics. These are based on the idea that Synthetic Biology is an emerging science with a huge potential and scope, making it necessary to invest in its development to build up the necessary intellectual and physical structures to capture a share of the valuable intellectual property that is at stake (see EC report, Synthetic Biology, a NEST Pathfinder Initiative, 2007).

The general principle of Synthetic Biology is the design of an artificial cell or even organism. Currently we are far away from this goal but indeed first attempts to reconstituting artificial cells from purified components and synthetic cell walls have already been reported. The areas of application covering a wide spectrum, from biological production and resources systems, like the design of engineered bacteria to photosynthesis of hydrogen or produce of saccharide, to medical sciences like cells engineered to generate reliable cell-to-cell communication or stable synthetic oscillator networks to mimic chronic disease.

The production of novel biological systems is also fostering the responsible development and application of next-generation biological technologies.

Although this scientific area is in its infancy, it is of utmost importance to further observe its development, because of the tremendous potential. Funding is needed to enable the establishment and maintenance of an 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 and design software for systematic testing purposes.

Close collaboration with social scientists is key to the responsible development of synthetic biology because of the profound ethical and public perception issues involved.

### 2.3.4 Chemical Biology

Compared to Cellular Biology, Chemical Biology is a relatively young discipline within the Life Sciences. Together with SB and Synthetic Biology it shares the interdisciplinary character. Originally born out of the biologist's and chemist's common interest in chemical strategies to investigate biological questions, this field has emerged as an important discipline in its own right.

Researchers in Chemical Biology find themselves at home in classical disciplines and study probe systems *in vitro* and *in vivo* with low molecular weight compounds (small molecules). Such molecules have been designed for a specific purpose or identified on the basis of biochemical or cell-based screening. They are used to discover and to analyse biological networks at different levels of complexity, which requires the perturbation of the activity of the involved molecular components of these networks by these small molecules. They serve as unique biochemical tools to study protein function by a dosage-, time- and spatially controlled perturbation of biological systems, complementing in an ideal manner the tools and technologies of molecular biology such as mutagenesis, antisense oligonucleotides, aptamers, and RNAi. Other results from this field, especially the identification of specific small-molecule agonist or antagonist available to modulate each protein function can be used for analysis in the frame of Systems Biology.

The Chemical Biology approach offers the possibility to systematically screen on a large scale basis for new bioactive agents for use in scientific research and industrial application. With Chemical Biology it is possible to address the wide variety of targets that emerge from genome research with small molecules. Thereby the knowledge in basic Life Sciences in general will increase and, based on that, novel commercial opportunities for Europe's future bio-economy in drug development will be opened. This is of utmost importance for the competitiveness of the European Research Area.

Screening facilities are currently mostly in industry and access for the scientific community and public sector in Europe is limited. Public sector facilities which do exist are fragmented. Although a number of national initiatives in various European countries (N, SP, UK, F. I, DE) have developed in the recent years, supporting the academic small molecule screening platforms and library synthesis centres, these platforms differ in their screening infrastructure, assay repertoire, compound libraries and data management. Nevertheless they have already built up a reasonably high degree of process automation in screening and/or chemical library synthesis, so that it is worth to invest in a RI on chemical screening platforms ensuring high quality control for the compounds and therefore reliability for the individual libraries through Standard Operation Protocols. This RI could make the libraries accessible to a much wider group of users in Europe and thereby address the BMS landscape puzzle.

### 2.3.5 Infectious, non communicable and ageing related diseases

There is a huge need in global healthcare for novel and innovative approaches to meet the needs of ageing populations and of people in less developed countries. This is a complex area of complementary interests and very diverse methodologies. There are still no known cures for half of the world's diseases, and even existing cures such as antibiotics are becoming less effective because of growing resistance to treatments. Biotechnology already enables cheaper, safer and more ethical production of a growing number of traditional as well as new drugs and medical services, e.g. human growth hormone without risk of Creutzfeldt-Jakob disease, treatment for haemophiliacs with unlimited sources of coagulation factors free from HIV and hepatitis C virus.

Nowadays the world faces the complex problem of a very large number of outbreaks of infectious diseases registered annually as well as a rising incidence of diseases associated to ageing, mainly in the developed world. Human tissues and body fluids may contain pathogens of high biosafety or biosecurity risk. Biobanking of these samples and their investigation is essential to study pathogen host interaction as a basis for new diagnostics and therapies. There is a need for biobanking of human biological samples containing moderate and high risk pathogens.

Health improvement has proven to be associated with sustainability of infrastructures that carry out research and with proper and wider dissemination of information on research achievements that support control measures. It is also strongly associated with related areas like (a) continuous surveillance, in case of migration of pathogens and fighting new epidemics, (b) regulatory matters concerning ethical issues in research methodologies and applications, (c) accessible repositories of pathogens that have great facility in changing themselves by mutations or accumulation of mutations often under the stimulation of outside known or unknown factors; (d) accuracy

of surveillance data from regions where new infections appear; (e) establishment of new diagnostic methods, whenever necessary, in all diseases (poverty, emerging, non communicable and ageing related); (f) improvement of quality of life systems aimed specially in the developing world, to age-related diseases and in proper distribution of drugs and vaccines.

The pathogenesis of age-related diseases is extended over large timescales. Illnesses start with a slowly progressing chain of molecular level events that are currently difficult if not impossible to detect. Therefore, early stage diagnosis opening avenues for effective therapeutical intervention is of utmost importance in challenging age-related diseases. This requires recruiting latest advances in physical instrumentation, modern imaging technologies, as well as high-quality chemical and biological resources.

The strategies of disease control affect all countries and their populations. Therefore exchange of data and dissemination of information on disease control and treatment is relevant in particular as an empowerment of the developing countries. Often emigration has been a major issue resulting in a loss of highly educated researchers. In the long run this unbalance will negatively affect us all. No infrastructure can be put at work in solving health problems without having a proper social program in training and communication with the developing world.

### 2.3.6 Marine Biology

Biological resources – living organisms, cells, genes, and the related information – are the essential raw materials for the advancement of biotechnology, human health, and research and development in the Life Sciences. Most of the evolutionary processes occurred from and in the oceans and a large number of marine organisms represent important models for studying evolution of developmental processes. The Marine laboratories, which encompass a representative European coastal ecosystem, represent a biological resource. The revolution in molecular biology has given us greatly increased ability to obtain and to modify these biological resources and to use them for the benefit humankind. The results of the different omics approaches in yeast and prokaryotic microorganisms has led to the conclusion that 'omics' research in marine organisms will gain huge insights in a lot of aspects of the functioning of life. These findings will have an unprecedented effect on the uses of biological resources particularly in synthetic biology and industrial biotechnology and the need for access to them; the demand will heavily increase. Marine biodiversity is important for assessing and monitoring of human impact on global ecology, for harvesting and production of food, for tackling fundamental questions in biology and for potential breakthroughs in biotechnology. Major challenges of mankind today are food supply and climate change. The development, expansion and survival of biological diversity faces many challenges.

For progress in both fields an up-to-date Marine Biology Infrastructure is indispensable to understand marine ecology and to explore novel marine molecular models. Therefore access to collections of cultivable organisms respective key marine microbial, algal or animals, replicable parts of these (e.g. genomes, plasmids, viruses, cDNAs) as well as databases containing molecular, physiological and structural information relevant to these collections is very important.

The merge of comparative and functional genomics with marine ecology and the new molecular approach to marine biology are two emerging fields of utmost importance to enable, through modelling of biological processes, more insights that could be beneficial to man. Hence the new information could also be used in SB approaches. Biological resource centres also play an important role in the preservation and provision of biological resources for scientific, industrial, agricultural, environmental and medical R&D and applications.

### 2.3.7 Food, Nutrition and Agriculture

Agriculture is now facing important challenges linked in particular to globalisation, consumer demands and environmental and food security concerns. As stressed by the Standing Committee for Agricultural Research (SCAR), established by European Council regulation, agriculture must cope with new pressures: a stronger demand for healthier food from consumers, a decrease of the genetic basis for food and agriculture, growing threats from new and emerging infectious diseases, a decrease of the genetic basis for food and agriculture, climate change and increased likelihood of abrupt changes in ecosystems, as well as major changes in rural areas linked to intensification and changes in activities, with the rise

of non-food agricultural production and conservation issues.

Research must adapt to these challenges and support the building of sustainable and competitive agricultural systems. To this aim, Europe needs to develop pan-European research capacities providing services to researchers who work on solutions. A few research infrastructures have been initially identified by SCAR as examples of strongly needed facilities. Among others are facilities for the study of infectious diseases, important for both the research on zoonoses and the research on human infections. Agriculture, forestry and environment observatories are another example of infrastructure that could be instrumental for the study of agro-ecological systems and the management of agricultural areas. Genetic, and biological resource centres for plant, animal, forest, aquatic and microbial resources, as well as resources in support of bioinformatics and systems biology approaches, are another example becoming central to studying agriculturally relevant organisms. As a last example, human nutrition research centres could be key to the development of functional foods.

These needs will need further attention by BMS RWG in the near future. The funding necessary to establish such required infrastructure indeed exceeds the financial and scientific capabilities of individual national research funding bodies.

## 2.4 BMS ESFRI Scientific Landscape

In the 21st century mankind is confronted with a wide variety of challenges arising from the rapidly increasing number of humans worldwide and aging people in Europe. Improving the health, including the increase of effectiveness in fighting emerging epidemics, as well as the growing demand for food and for bioresources are the future topics. Life Sciences infrastructures can contribute to the solution of these important questions:

It is clear that the current century is the „century of Life Sciences“. Due to the rapid development of technology in this area tremendous possibilities are opened up to answer basic biological questions leading to progress in applied sciences and thus to an improvement in prosperity and life quality for all mankind.

### 2.4.1 Current RI initiatives

Characteristic of the work of all modern scientists, independent from their scientific background, is the tremendous amount of data produced. Bio-informatics is more than ever a prerequisite for both experimental and applied biology. In turn the production of the data is strongly coupled to 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 basis. These methods originate from the DNA recombinant technology accompanied by high-throughput analytic techniques. This is the reason for the deep transformation process the Life Sciences have undergone since the 1980’s and still are undergoing.

Modern Life Sciences are inconceivable without access to well structured, continuously upgraded and freely accessible databases. The BMS research community relies on exchanging data and information from distributed and heterogeneous sources. One of the main challenges is to develop the infrastructures required to ensure that these data have been collected in harmonised ways and made accessible to the research communities.
With the implementation of **ELIXIR** European RI in this field will be developed to address these needs. ELIXIR is one of the six RIs already on the ESFRI RM and is strongly interconnected to all other five RIs, which all complement each other and have one overall goal in common, the improvement of health.

The pan-European Biobanking and Biomolecular Resources Research Infrastructure **(BBMRI)** is collecting Human biological samples, such as blood, tissues or DNA. They also include associated clinical and research data, as well as biomolecular research tools, which are key resources in unravelling genetic and environmental factors underlying diseases and influencing their outcome. These resources are required for identification of new targets for therapy and may help to reduce attrition in drug discovery and development. BBMRI is strongly cooperating with **EATRIS**, which is dealing with translational research. The translation of basic research discoveries into clinical applications, including the scientific validation of experimental results, should support a faster and more efficient translation of research findings into the development of innovative strategies for the prevention, diagnosis and treat-

ment of diseases of particular relevance for European member states and that have a high medical and economic burden.

There is a strong connection of EATRIS with **ECRIN** as ECRIN follows EATRIS on the development chain of new therapies and diagnostics. ECRIN deals with clinical trials from phase II onwards whereas EATRIS covers the research up to clinical trials phase II. The collaboration between both RIs facilitates the transfer of innovative interventions into improved medical care and health strategies.

Having a similar goal, but coming from a different edge of science, **Infrafrontier** is dealing with functional genomics and mouse genetics. Since the mouse genome was completely sequenced and it became clear that the differences in the genome between mouse and man is very little the mouse was established as a model organism for human diseases. In the 21st century 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 is expected, so that tens of thousands of mouse disease models will become available, all of which will ultimately require archiving, dissemination and phenotyping. Therefore the necessity is evident for a close cooperation with respect to data management (ELIXIR), with Biobanks (BBMRI) and, with respect to the design of animal facilities, with EATRIS.

**INSTRUCT** is combining integrated Structural Biology with cell biology, leading to the study of more complex systems within the cell and starting from the study of single protein molecules, thereby bridging the gap between genetic information and its use in therapeutic interventions. It strongly is cooperating with ELIXIR and RIs of the PSE.

Although the first set of RIs originates from different areas in the BMS field and cover a wide variety of methods and technology, they all have in common the basic requirements needed such as data management and imaging technologies. They also have to face other common problems originating from standardisation and harmonisation approaches, ethical issues etc. Therefore they will all work closely together and establish common working group or mutual exchange on overlapping interests.

BMS RWG was led by three aspects in updating the scientific landscape. First for all future RIs it is important that the basic tools required to generate optimal results are provided, e.g. ELIXIR and Imaging technologies. Second, the RIs already being on the RM need to be strengthened through filling the gaps in health research that still exist and thereby provide a much more efficient output as it can currently be reached. The third important aspect was the completion of the landscape through widening the scope to a) cover problems and fields currently not considered (e.g. food) and to b) integrate the research areas, forming the basis of biological resources and the basis of basic research (e.g. Marine Biology).

### 2.4.2 Potential future RIs initiatives

Over the last 2 years since the first ESFRI RM was published, the main development in the BMS field was the increased demand for novel interdisciplinary approaches including biological and functional imaging and chemical biology. The BMS RWG aims to establish RIs, which fill the gaps currently existing.

One of the basic needs in Life Sciences, essential for all scientific fields from basic biology as Cellular or Developmental biology through applied science in medicine is the access and the development of novel **Imaging Technologies.** The recent developments of advanced light microscopy methodology and biomedical imaging have been rapidly proceeded within the last decades accompanied with the explosion in the use of digital imaging techniques especially used in basic research. The challenge for biomedical imaging is 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.

A great chance for the scientific community as well as for industry is the research area of **Chemical Biology**, which deals with studying probe systems in vitro and in vivo with low molecular weight compounds (small molecules). This approach offers the possibility to systematically screen on a large scale basis for new bioactive agents covering a wide range of areas from human and veterinary medicine, to agriculture and nutrition. New findings in this field, especially the identification of specific small-molecule agonist or an-

tagonist available to modulate each protein function could directly be used for analysis in the frame of Systems Biology.

In the context of emerging and re-emerging infectious diseases involving highly pathogenic micro-organisms there is a real need for Europe to be prepared to face such a potential threat. In the case of H5N1 threat, no human cases have so far been detected in Europe and no inter-human contaminations have been demonstrated. However, in contrast, the pandemic outcome of SARS and avian flu epidemics has represented worldwide threats. Also viral haemorrhagic fevers such as Ebola and viral encephalitis like Nipah could have a major burden on socio-economic development in the developing countries and through migrations and global travels increasingly threaten the population of Europe. These emergences have demonstrated the need to work on highly infectious pathogens, making it necessary to establish a RI of **High security laboratories**.

Europe has a distinguished history in **Marine Biology** with many marine biological stations established in the late 19th Century. They support the needs of the scientific community in basic biology, marine biology and ecology by developing and applying new technologies using molecular biological and genomic approaches. The demand for marine organisms used as models to investigate fundamental questions in biology is constantly increasing. The marine biological stations provide access to these organisms. The results from experimental work in biomedicine, biochemistry, physiology and systematics can further be used in areas like aquaculture and in the development of sustainable new materials and processes, e.g. medicines and bio-fuels.

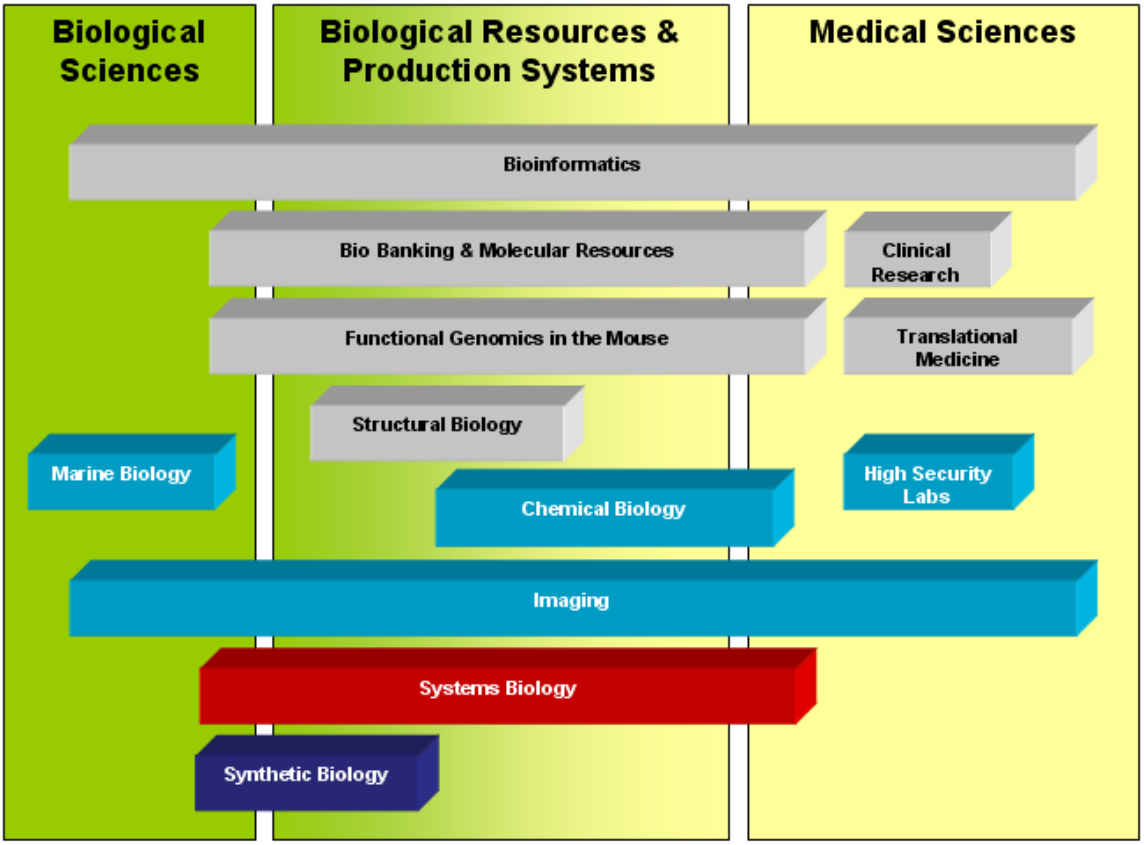



Diagramme: Landscape of BMS RIs

### 2.4.3 Future perspectives

Today biologists can obtain a tremendous insight in the functions of life. Because of major progress achieved through, e.g., genomics and modern RNA-based 'reverse' genetics, it is possible to study in depth not just simple systems - such as viruses and microbes - but

virtually any organism, including humans. Thus the importance of understanding of how various systems work, what they have in common and what is different and how processes of life and their variations have survived the evolutionary process has increased. This knowledge can be used to design new cures and effective interventions. It opens up ground breaking new dimensions, e.g. the production of completely artificial biological systems from individual molecules to whole cells, tissue and even organisms in the new field of research called **Synthetic Biology.**

Another field benefiting from this knowledge is **Systems Biology**, which tightly integrates high through-put experimental approaches in molecular biology, biochemistry and chemistry together with bioinformatics, novel physics and engineering technologies, through mathematical approaches, including modelling and simulation. SB approaches, by integrating Bioinformatics and modelling of genomic data, attempt to predict and explain the functional architecture of genomes across the diversity of organisms. Systems Biology provides the analytic framework in which Synthetic biology operates, by developing the high-throughput/high –resolution type of analysis on which Synthetic Biology depends. Both fields will be of huge importance for the future.

Currently Life Sciences operates through a transition on the one hand from traditional models (e.g. worm, fly) to target organisms (e.g. mammals) and on the other hand from the level of discovering molecules to understanding of how whole organisms function. Therefore biological resources are considered as the essential raw material for the advancement of biotechnology, human health and research and development in Life Sciences. There is an evident need for additional **Biological Resource Centres** that focus on the collection and distribution of materials and reagents for the study of species other than humans (animals, plants, bacteria). These new centres would complement the BBMRI RI and thereby further strengthen the European RI in the future.

**Biomedical engineering** is a fast developing area which crosses Life Sciences, engineering and material sciences. Biomaterials stand as a potential solution not only for medical applications but also many other biotechnological applications including sensors that would help monitoring and cleaning biohazards. Tissue engineering is a young field which could ultimately unite synthetic and “natural” cells on suitable scaffolds into new organs etc. Biomechanics and advances in mechatronics will have a future role in supporting the needs and health of the aging population including artificial replacement of bone and other structural tissues. Brain computer interface and similar applications of the future can become means to increase the quality of life, finding applications from the usage in cases of disability to even industrial production lines. Accordingly, state of the art RI’s are needed to organize, stimulate and amalgamate cross disciplinary efforts into world leading scientific and technological leaps for Europe.
The European Innovative Medicine Initiative (**IMI)** platform is designed to address the health and biomedical research challenges of the 21$^{st}$ century. The efficient implementation of the IMI Strategic Research Agenda requires the development of appropriate RIs providing high quality and certified services. Three of the six BMS RIs on the ESFRI RM have been identified to be of particular interest for the IMI platform (ECRIN, EATRIS and BBMRI). A recent meeting allowed coordinators of these three ESFRI-BMS RIs, representatives of the IMI platform and of the European Commission to initiate a coordinated approach between IMI and the ESFRI RIs. This cooperation will be strengthened and increased in the future.

Finally, particular attention will need to be given to identifying and supporting the new infrastructure requirements of agricultural research. Agriculture is indeed facing important challenges linked in particular to globalisation, consumer demands and environmental concerns. Future BMS work will in particular incorporate the outcome of the infrastructure analysis currently carried out by the Standing Committee for Agricultural Research (**SCAR**).

# 3 PROGRESS OF THE 6 RIs IN THE PREPARATORY PHASE

## 3.1 Introduction

After the first ESFRI RM was published in October 2006, the EC decided to support the "preparatory phase" for the preparation of the RIs of the ESFRI RM through their first FP7 Research Infrastructure call for proposals. The main goal of this action was to provide catalytic and leveraging support, helping RIs to reach the level of technical, legal, and financial maturity required to enable their construction.

The call closed at the end of April 2007. The evaluation results of the six BMS proposals were exceptional, five out of the six Life Sciences proposals reached the highest score, and these were five of the six highest scorers across the call as a whole. The sixth BMS proposal reached the third highest score. This result demonstrated, that all 6 Life Sciences proposals showed high maturity in the frame of the ESFRI criteria and that they would contribute to the competitiveness of Europe's industry and support the achievement of the Lisbon targets.

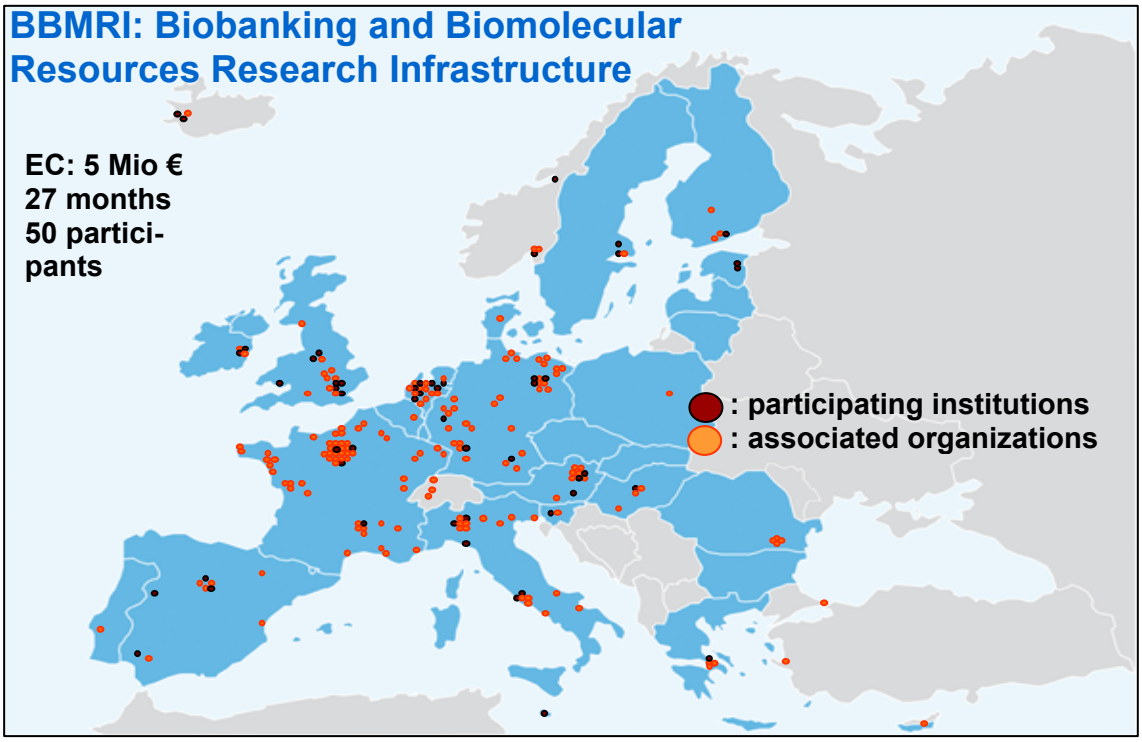
One of the tasks of the BMS RWG is to deliver an ongoing strategic process to help ESFRI to implement the RIs already on the RM already (incubator role). One aspect of this role is supporting the consortia and giving advice. At the 10th BMS RWG meeting in December 2007 it was decided to prepare a template, similar to the first one used to apply for inclusion on the ESFRI RM, to ask for the current status of the RI, including the pp, which is still a part of the implementation of the RIs. The results of the survey are shown in more detail in the next part of this report.

One of the tasks of the BMS RWG in the incubator role is to guarantee the exchange of experiences between the 6 coordinators of the RIs and to strengthen the cooperation between the RIs. To address this, a coordinators meeting was organised in June 2008 in Brussels.

## 3.2 RIs

Most of the consortia started their negotiations for the pp in summer 2007 and began their work from November 2007 to April 2008. The kick-off meetings were mainly being held during December 2007 and June 2008. In most cases the pp was calculated to run for three years. The number of partners within these consortia varies between 17 and 50 and the EC contribution is between 4.2 and 5.8 Mio €. Detailed information is included for each RI in the next chapters. Most of the data were kindly provided by J.-E. Faure (EC).

### 3.2.1 Biobanking and Biomolecular Resources Research Infrastructure (BBMRI)




The draft proposal for the establishment of a European Biobanking and Biomolecular Research Infrastructure (BBMRI) was presented at the Partner and Stakeholder Meeting in Vienna (Austria) on March 17th, 2007 to a broad scientific and stakeholder community. The comments of participating parties have been considered in the final proposal that was submitted to the European Commission on May 1st, 2007. The proposal was accepted by the European Commission and 5 Mio € funding for a 27 months preparatory phase for BBMRI has been negotiated. The starting date of BBMRI was February 1st, 2008 and the kick-off meeting was held at Hinxton, UK on February 10th-12th, 2008. By July 2008, the consortium consisted of 50 participants (including 21 funding organizations) and 182 associated organizations from 27 European countries, including Israel, Australia, the Faeroe Islands and Saudi Arabia.

BBMRI will build on existing sample collections, resources, technologies, and expertise, which will be specifically complemented with innovative components. In particular, BBMRI will comprise i) all major population-based and disease-oriented biobank formats, ii) bio-molecular resources, such as collections of antibodies and other affinity binders and a variety of molecular tools to decipher protein interactions and function, iii) bio-computing and sample storage infrastructure. All resources will be integrated into a pan-European distributed hub structure-like network, and will be properly embedded into European scientific, ethical, legal and societal frameworks. Specific tasks in the planning of BBMRI are the preparation of an inventory of existing resources, implementation of common standards and access rules, establishment of incentives for resource providers, and to develop solutions for international exchange of biological samples and data which properly consider the heterogeneity of pertinent national legislation and ethical principles.

BBMRI will also develop biobanking solutions for and provide access to biological samples for the Life Sciences RIs INSTRUCT, INFRAFRONTIER, EATRIS and ECRIN. The bio-computing infrastructure for BBMRI will be established in close collaboration with ELIXIR and by considering future capacities of the e-Infrastructure.

## 1. Name and descriptive title

**BBMRI - Biobanking and Biomolecular Resources Research Infrastructure**

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

Human biological samples, such as blood, tissues or DNA, plus associated clinical and research data, as well as biomolecular research tools are key resources in unravelling genetic and environmental factors underlying diseases and influencing their outcome. Furthermore these resources are required for identification of new targets for therapy and may help to reduce attrition in drug discovery and development. Consequently, biological resources are considered as the essential raw material for the advancement of biotechnology, human health and research and development in life sciences. The pan-European Biobanking and Biomolecular Resources Research Infrastructure (BBMRI) is designed to further develop these resources and to provide access to academia and industry.

The Preparatory Phase focuses on technical, legal, governance, and financial issues to

- prepare to construct BBMRI, building on existing biobanks, resources and technologies, specifically complemented with innovative components and properly embedded into European scientific, ethical, legal and societal frameworks,
- provide the concept for a key resource to increase excellence and efficacy in biomedical sciences, drug development and public health,
- expand and secure competitiveness of European research and industry in a global context and
- develop a sustainable financial framework.

Biomedical quality-assessed samples and data as well as biomolecular resources and molecular analysis tools are essential for academic and industry-driven research to treat and prevent human diseases.

BBMRI will be composed of a network of centres organized in a distributed hub structure comprising:

- biobanks of different formats (collections of blood, DNA, tissue, etc., together with medical, environmental, life-style and follow-up data),
- biomolecular resources (antibody and affinity binder collections, ORF clone collections, siRNA libraries, proteins, cellular resources etc.),
- enabling technologies and high-throughput analysis platforms and molecular tools to decipher gene, protein and metabolite functions and their interactions,
- harmonized standards for sample collection, storage, pre-analytics and analysis,
- harmonized databases and biocomputing infrastructure and ethical, legal and societal guidance platform.

## 3. Science case

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. Innovative, high-throughput technologies are widely expected to enable a better dissection of these complex, causally heterogeneous diseases into more specific diagnostic entities, which is a requirement for the advancement of personalised medicine. A sharper, biology-based definition of disease categories will enhance the development of more effective treatment, reduce undesired side effects of new treatments, improve success in clinical trial design, and will lead to new concepts of disease prevention. Elucidation of complex disease aetiology is challenging because diseases are caused by a large number of small, often additive effects, representing the sum of the consequences of genetic predisposition, lifestyle and the environment.

Revealing these complex interactions will depend critically on the study of large sets of well-documented, up-to-date epidemiological, clinical, biological and molecular information and corresponding material from large numbers of patients and healthy persons, collected and made available by biobanks. The biological material collected in biobanks for biomedical research typically comprises DNA, tissues, cells, blood or other body fluids. Although currently established biobanks and biomolecular resources are a specific European strength, valuable and irreplaceable national collections typically suffer from fragmentation of the European biobanking-related research community, variable access rules and the lack of commonly applied standards. This hampers the collation of biological samples and data from different biobanks which is a prerequisite to achieving sufficient statistical power.

Moreover, it results in duplication of effort and jeopardises sustainability because of the lack of long-term comprehensive funding approaches. There is also a need to strengthen the capacity to develop networks of biobanks meeting high standards of integration compatible with the design of studies structured as Phase II or III clinical trials. This type of study design is essential for validation and translation of biomarkers into clinical practice.

Ultimately, this will favour the study of important biomedical research questions that are beyond the scope of a single effort. Short-term benefits of a pan-European research infrastructure will appear soon, such as increased quality and reduced cost of research through better coordination, while longer perspectives include increased efficacy of drug discovery and development, and finally novel possibilities in health care (such as personalised medicine) and secured European competitiveness in research and industry.

## *4. The Concept case*

Key components of BBMRI are comprehensive collections of biological samples from different (sub-) populations of Europe, which should be linked with continuously updated data on the health status, lifestyle and environmental exposure of the sample donors. This can only be achieved in a federated network of centres established in most, if not all, European Member States. Therefore, the format of BBMRI should be a distributed hub structure in which the hubs coordinate activities, including collection, management, distribution and analysis of samples and data for the major domains. The biobanks, biomolecular resources and technology centres, which are members of BBMRI, are associated with their specific domain hub. Furthermore, a variety of public or private partners (e.g., universities, hospitals, companies), which provide biological samples, data, technologies or services, may be associated with certain BBMRI members.

- BBMRI members represent the key providers of resources and technologies. Members are leaders in the field and drivers of innovation and scientific excellence. Membership is non-exclusive so that members link BBMRI to other national, European (e.g., other FP7 programs) and global initiatives (e.g., the emerging OECD global network of Biological Resource Centres or WHO programmes).
- Associated partners and subcontractors provide certain resources (services, data, samples, materials) to BBMRI. An associated partner, for instance, a hospital or research institute which provides biological samples and data, may be either reimbursed or compensated for its contribution by being granted free access to resources and technologies of the BBMRI. Associated partners may also be ministries, governments, research councils, and funding agencies from interested countries whether or not they currently support biobank or biomolecular resource infrastructure projects
- Users may come from different fields of academia and industry. Access will be provided in the context of specific research projects and on the basis of secured funding. Incentives may be provided for EU Member States and for industry to enter into general user agreements.

This structure provides great flexibility so that new members and partners can be connected at any time and so that it can be adapted to emerging needs in biomedical research. The IT infra-

structure which employs federated database architecture and grid computing technology will integrate the complex network of hubs, members and partners. Hubs will be coordinated and directed by an executive management, which is supported by a governance council as well as by a high-calibre advisory board and receives input from the stakeholder forum to guarantee clear responsibilities as well as open and transparent decision-finding processes.

BBMRI will link to several ongoing international activities, such as those pursued by P3G, the Innovative Medicines Initiative, ISBER, the OECD, and the WHO, as well as research projects funded under FP5/FP6 and new projects under FP7. To avoid duplication of activities, BBMRI will exchange concepts and experience with these activities.

## *5. Further information, including strategic importance to ERA*

Over the last two decades, Europe has lost some ground in scientific issues, especially in the life sciences. The global networking component of BBMRI will ensure that what will be developed in Europe will have an important global impact. Europe will serve as a model for other regions and thereby enhance its scientific credentials. Other regions and international institutions will be given new and improved implementation modules for their own development. To balance the need, on one hand, for Europe to retain leadership in science and, on the other, to provide global solutions, thus sustaining the development and the use of biological resources, is one major aim of this project.

BBMRI will contribute to the technological development capacity in ERA by creating an infrastructure that also has a focus on research and development in sample and data management processes. In existing infrastructure components, such research and development has tended to take second place to the pursuit of investigations into the biological resources themselves, rather than into their management. As a result, improvements in basic laboratory processes (e.g. purification techniques) have tended not to be developed beyond proof of principle and data management systems have been developed with single locations in mind. The BBMRI Preparatory Phase will plan coordination between these infrastructure components and create a unique body of expertise with the capacity to make such improvements.

BBMRI will contribute to the scientific excellence of Europe as a whole by

- providing access by investigators to high quality biological resources and data,
- supporting training of a new cadre of professionals in biobanking,
- participating in current and future national EU framework programme health research projects,
- enabling synergies between epidemiologists, clinicians, geneticists, pathologists and molecular biologists in national centres of excellence,
- partnering with the pharmaceutical, biotech and computing industries.

BBMRI will provide a competitive advantage and fruitful environment for development of service and technology companies by acting as an R&D partner as well as a customer.
The implementation and development of its “distributed hub structure” is designed to allow the extension of the infrastructure by incorporating existing and new components that meet the criteria of excellence of BBMRI and that have physical locations in the convergence regions as well as the outermost regions thus providing a pan-European solution.

## *6. Identification of other socio-economic impacts*

BBMRI will speed up development of personalised medicine and disease prevention and will embrace some of the needs of basic research as well as of the biotech and pharmaceutical industries. Thus it will enable improvements in public health and will help some bottlenecks in the drug discovery and development process. BBMRI will strongly boost political and scientific momentum to harmonise ethical, legal and quality standards across Europe.

BBMRI will contribute to EC policy developments by
- harmonising existing standards,
- providing opportunities for integrated transnational education and training,
- preparing the ground for harmonized legislation with respect to use and exchange of biological samples,
- leading to harmonization of funding schemes throughout Europe to provide sustained funding to guarantee maintenance of and access to key resources.

## 7. Participating Members

Scientific Partners
**29**

- Medical University of Graz, Austria
- National Public Health Institute, Finland
- National Research Center for Environment and Health, Germany
- Uppsala Universitet, Sweden
- Karolinska Institutet, Sweden
- University of Manchester, United Kingdom
- International Agency for Research on Cancer, France
- Academisch Ziekenhuis Leiden, The Netherlands
- Norwegian University of Science and Technology, Norway
- Semmelweis University, Hungary
- EGP of the University of Tartu, Estonia
- National DNA Bank, University of Salamanca, Spain
- Helmholtz Gemeinschaft, Germany
- VITRO Ltd, Spain
- Ensembl Functional Genomics, European Genotype Archive, United Kingdom
- Erasmus MC Rotterdam, The Netherlands
- Istituto Nazionale per la Ricerca sul Cancro, Biological Bank and Cell Factory, Italy
- Institute for Biomedical

Funding Organisations (ministries, research councils)
**21**

- INSERM, France
- University of Malta, Malta
- Fondazione Telethon, Italy
- Féderation hospitalière de France – FHF, France
- Irish Clinical Research Infrastructure Network, Ireland
- Institut National du Cancer, France
- Comitato Nazionale per la Biosicurezza, le Biotecnologie e le Scienze della Vita, Istituto Superiore di Sanita, Italy
- Max-Planck-Institut für Molekulare Genetik, Germany
- Instituto de Salud Carlos III, Spain
- Norwegian Institute of Public Health, Norway
- Research Infrastructure and Special Initiatives Unit Health Research Board, Ireland
- Medical Research Council, United Kingdom
- Ministry of Education, Culture and Science, The Netherlands
- The Icelandic Centre for Research, Iceland
- The Netherlands Organisation for Health Research and Development, The Netherlands
- Fraunhofer IBMT, Germany
- Bundesministerium für Bildung und Forschung, Germany
- Bundesministerium für Wissenschaft und Forschung, Austria
- Alleanza Contro il Cancro, Italy
- Fundación para el desarrollo de la investigación en Genómica y Proteómica, Spain

Associated Partners
**182**
**organizations**

| | |
|---|---|
| Austria | 7 |
| Australia | 1 |
| Belgium | 1 |
| Canada | 1 |
| Faroer Islands | 1 |
| Finland | 2 |
| France | 57 |
| Germany | 30 |
| Greece | 3 |
| Hungary | 3 |
| Iceland | 2 |
| Ireland | 2 |
| Israel | 1 |
| Italy | 17 |
| Malta | 1 |
| Norway | 2 |
| Poland | 1 |
| Portugal | 1 |
| Romania | 4 |
| Saudi Arabia | 1 |
| Slovenia | 1 |
| Spain | 6 |
| Sweden | 2 |
| Switzerland | 3 |
| The Netherlands | 20 |
| Turkey | 2 |
| UK | 10 |

| | | |
|---|---|---|
| Technologies, Italy<br>• UK Biobank Ltd, United Kingdom<br>• University Hospital Groningen, The Netherlands<br>• Dutch Federation of University Medical Centers, The Netherlands<br>• Legal Pathways b.v., The Netherlands<br>• deCODE genetics, Iceland<br>• Life Science Governance Institute, Austria<br>• Center for Economics and Social Aspects of Genomics, United Kingdom<br>• Babraham Bioscience Technologies, United Kingdom<br>• Hellenic Republic Ministry of Development, General Secretariat For Research & Technology, Greece<br>• Biomedical Research Foundation of the Academy of Athens, Greece<br>Universitaet Klagenfurt, Austria | • Ministry of Education and Research, Estonia | |

***8. Budgetary information***

| | | | |
|---|---|---|---|
| Preparatory cost<br>5 Mio € | Construction cost<br>approx. 170 Mio €<br><br>to be further determined in the preparatory phase | Operation cost (total)<br>approx. 15 Mio €/year<br><br>to be further determined in the preparatory phase | Re- and decommissioning cost (total in Mio €)<br><br>Not applicable |

***9. Timetable until operation***

| | | | |
|---|---|---|---|
| Preparatory phase<br><br>27 months | Construction phase<br><br>12 months for core network<br>36 months for fully established infrastructure | Operation<br><br>20 – 30 years | Re- and Decommissioning<br>Not applicable |

## *10. Contact*

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Austria
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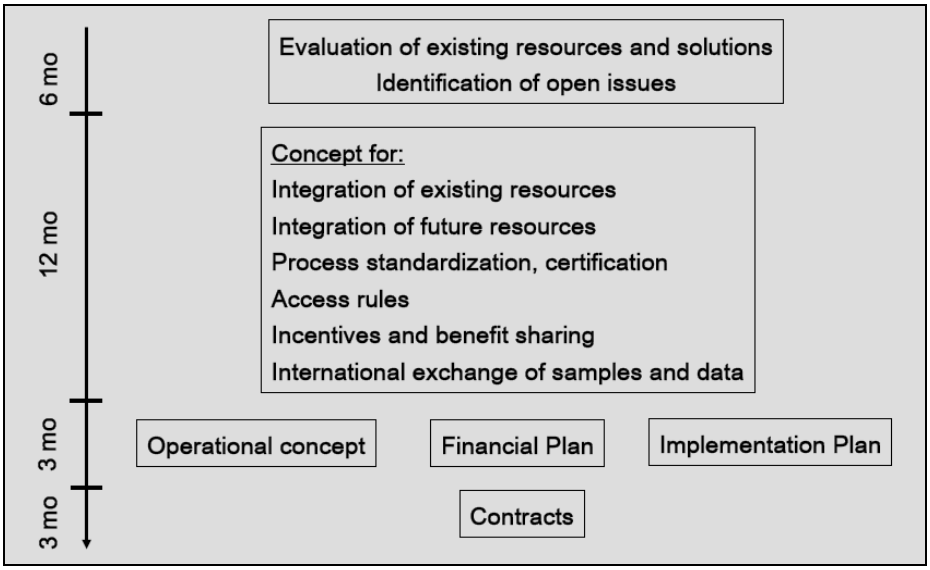
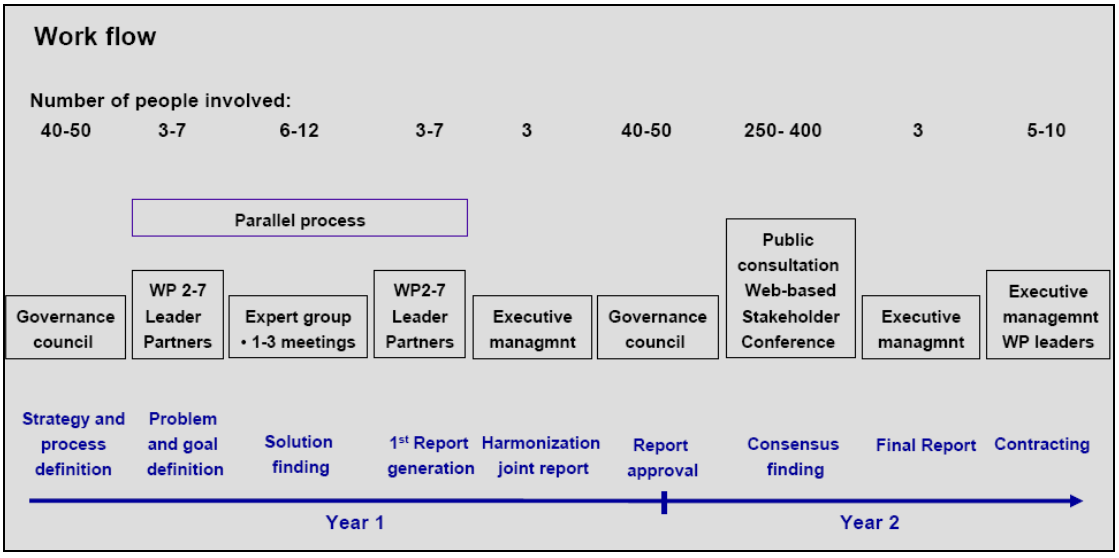
www.bbmri.eu

## *11. Progress in the preparatory phase*

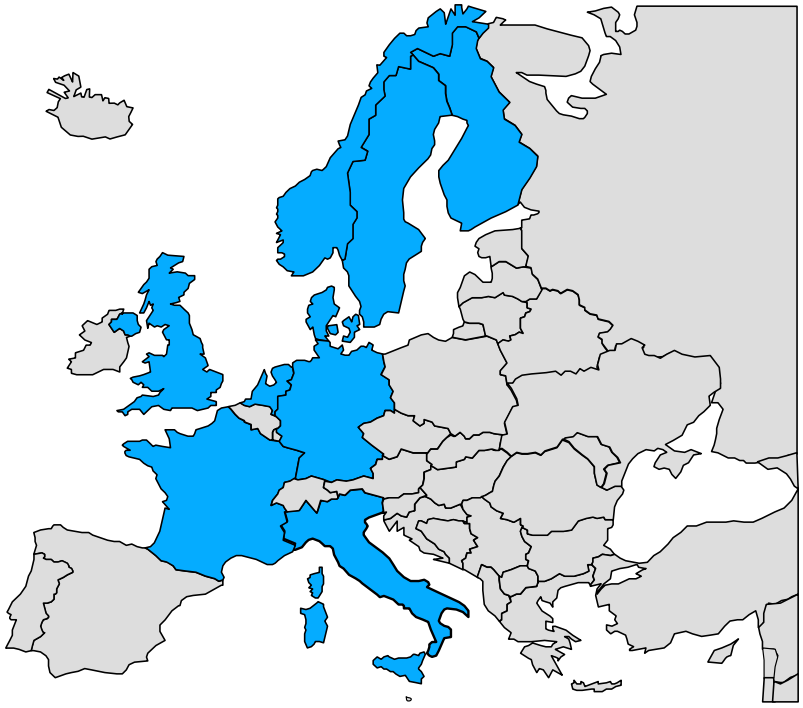


### 3.2.2 European Advanced Translational Research Infrastructure in Medicine (EATRIS)

**EATRIS: European Advanced Translational Research Infrastructure in Medicine**

**EC: 4.2 M€**
**36 months**
**17 partners**
**www.eatris.eu**



Efficient translation of research discoveries into industrial application is an essential element to maintain Europe's competitiveness in the biomedical and health industry. The main bottleneck is the inadequate and fragmented nature of essential research infrastructure and know-how, leading to unacceptable delays and/or prevention of the development of new innovative medicines. The aim of **EATRIS** is to fill this gap by developing a **E**uropean **A**dvanced **T**ranslation **R**esearch **I**nfra**S**tructure consisting of key preclinical and clinical components necessary to support the development of new diagnostic or therapeutic strategies at all stages of the biomedical R&D-process.

EATRIS will operate through a network of biomedical translation research centres across Europe which will provide user access to modern interdisciplinary research labs and expert know-how in a unique under-one-roof approach which allows exchange of knowledge and goals forwards and backwards along the development chain. In addition, high quality services will allow a targeted complementary service to the research community.

Users of EATRIS will be biomedical researchers and clinical scientists located at universities, research institutions or SMEs that need to use this infrastructure in order to overcome specific bottlenecks and to move their research projects from a discovery to a preclinical and clinical stage.

After the adoption of the ESFRI RM in September 2006, a first meeting of the relevant players in the area of translational research as nominated in the RM took place in January 2007. The aim of the meeting was to define the scope of a future translational research infrastructure and to outline the basic concept of a proposal for a Preparatory Phase. First criteria for an extension of EATRIS to more partners and countries were defined. During the proposal preparation Finland, Italy, and Norway decided to join the EATRIS consortium along with the support of their relevant ministry or funding agency as the extension

policy of EATRIS requires. Currently EATRIS comprises 10 research organisation and 11 funding bodies (of which 3 are Associated Partners), several new countries are in the process of entering the consortium.

The EATRIS proposal was selected by the European Commission and granted 4,2 Mio € for a 3 years funding of the Preparatory Phase. During this phase, EATRIS will develop a best practice concept of translational medical research which aims at the provision of research infrastructure in an open and interdisciplinary research environment as well as the integration of central facilities. In EATRIS, the facilities, services and knowledge needed for efficient translational research on a European level will be characterised. A master plan will also include the legal, financial and organisational aspects of the infrastructure.

Before the contract came into force on 1st January 2008, a meeting of all partners was held in September 2007 to prepare the documentation for negotiation and the consortium agreement and to define the working mode.

The kick-off meeting took place in March 2008, when the Steering Committee also met. The extension policy for the EATRIS policy phase was officially adopted and the first new partner to the consortium was accepted. As a rule, only countries with a documented interest in translational research can join EATRIS. An advisory board was set up which comprises high-level representatives of all stakeholder groups like regulatory bodies, pharmaceutical industry, SMEs, funding bodies, researchers and patient associations.

At the kick-off meeting, the different work packages also had their first meeting to further organise their work and agree on the work schedule. EATRIS will hold a survey on translational research in Europe and the need of users for translational research infrastructures during the first half of 2008.

### *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*

The enormous progress made in biomedical research during the last two decades bears a tremendous medical and economic potential. Exploiting this potential however has been much more difficult than expected. **Translation of basic research discoveries into industrial application has turned out to be a major challenge for the European Research Area.** A major bottleneck is the fragmented nature of basic and clinical research infrastructure, leading to unnecessary delays and difficulties in drug development or the implementation of new diagnostic strategies.

**EATRIS is a distributed pan-European infrastructure consisting of a network of biomedical translation research centres** across Europe. The aim of EATRIS is to support a faster and more efficient translation of research findings into the development of innovative strategies for the prevention, diagnosis and treatment of diseases which are of particular relevance for European member states and that have a high medical and economic burden.

EATRIS will provide access to preclinical and clinical research infrastructure to bridge the gap between basic biomedical research and clinical application. This infrastructure will consist of a number of physical components which include state of the art **animal facilities** for preclinical validation studies, **small molecule screening facilities** to identify and characterize new drug targets, disease specific **patient and population cohorts** to develop and validate new hypotheses for innovative diagnostic and therapeutic strategies, **centralized GMP facilities** for bioprocess development and manufacturing, and facilities to carry out clinical phase I studies. In addition, there will be **training facilities and programmes** specifically dedicated to translational research. EATRIS translation centres will thus provide an ideal environment for

exploiting the potential of an interdisciplinary cooperation between basic and clinical research. The users of the EATRIS infrastructure will be basic biomedical researchers and clinical scientists located at universities, research institutions or SMEs and industrial partners that need support in order to overcome specific bottlenecks and to move their research projects from a discovery to the preclinical and clinical stage. EATRIS will offer a unique package of services for European Scientists consisting of access to state of the art facilities needed for translation research and professional expert consultancy services. The EATRIS infrastructure will comprise all **facilities necessary to assess safety and efficacy of potential new drugs on all stages from basic research to phase I clinical studies.** The consulting services will include an assessment of the scientific basis, issues related to intellectual property rights, advise on regulatory issues, benchmarking with regard to existing technologies, potential risks, market potential, cost, medical need and ethical issues. EATRIS will also play an important role in the training and education of the next generation of translation researchers, a major bottleneck also identified by the European technology platform IMI (Innovative Medicine Initiative). A special work package will be dedicated to the development of an integrated concept where the EATRIS infrastructure is utilized for training and education.

EATRIS will initially cover the following five **disease areas**: cancer, metabolic diseases, neurological disorders, cardiovascular diseases and infectious diseases. For each of these disease areas one or more centres take on the responsibility to provide to the research community infrastructure essential for translation in a specific disease area. One disease coordinator will be nominated for each disease area. He/she will coordinate the disease specific aspects of translation within EATRIS and with other European researchers. Once EATRIS is successfully established, an extension considering other diseases is planned.

As a whole EATRIS will provide a central gateway for essential infrastructure necessary for translational research and form a nucleus for the development of European Translational Medicine.

### *3. Science case*

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. 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.

Translation of laboratory findings into diagnostic, therapeutic and preventive clinical applications 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.

The current concept for EATRIS is to provide an infrastructure suited to overcome the current bottlenecks of translational research.

- Inefficient transfer from target identification to clinical validation
- Need of specialised equipment and services
- Lack of preclinical predictivity of safety and efficacy

- Lack of communication between clinical & basic scientists
- Lack of standardised measuring and data management procedures
- Paucity of clinical and basic scientists with training in translational research

The core of EATRIS will be a network of dedicated translational research centres across Europe, which will provide the infrastructure components necessary for translational research. Each centre will be characterised by integrating the physical components into an environment where clinical scientists and basic scientists cooperate **"under one roof",** creating a productive working environment and research culture for translational medicine.

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 centres 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 centres will advance translational research to a substantially greater extent than centres funded to do their own research. The consortium centres 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.

### *4. The Concept case*

So far translational medical research is organised individually by the research institutions or SMEs. There is no national coordination of such activities, thus not even the synergy of existing facilities is being exploited. Often a lack of knowledge can cause unnecessary delays and wrong strategies, due to the lack of infrastructure some good approaches are not taken up.

EATRIS aims to build on existing translational centres to build up a European network of translational infrastructure and excellence. The strategy is to use and up-grade available facilities to allow a smooth and flexible transition and at the same time strengthen and complement the current translational research infrastructures to gain maximum benefits. New centres will follow a best practise example of established core centres.

A major goal of EATRIS is to build up an efficient national coordination. The aim is to integrate existing facilities which could contribute to the infrastructure and to respond to national or regional demands. Supra-regional infrastructure which does not have to be provided locally will complement the range of services. This is supposed create the best possible synergy in medical translational research.

In addition to national coordination, EATRIS also introduces a disease-oriented approach to respond specifically to requirements of those fields, thus reducing double work and channelling resources. At first, EATRIS will focus on the following diseases:

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

EATRIS will stimulate European cooperation in the field of medical translational research.

Apart from the mandate for a national integration fulfilled by the core centres, it is aimed to include more countries. EATRIS is open for partners from other countries already in the preparatory phase. After the preparatory phase, the legal entity of the EATRIS research infrastructure will invite more interested centres to join if they fulfil the criteria and quality standards agreed upon in the preparatory phase.

For the physical infrastructure of EATRIS, the following key components have been identified:

**i Animal facilities**

Animal facilities will be designed, that are able to specifically address the requirements for a preclinical safety and efficacy evaluation of drug candidates. These animal facilities will have a disease specific focus, but will also be equipped to carry out detailed phenotyping of a wide range of basic and general clinical parameters. A close interaction will take place with the INFRAFRONTIER ESFRI BMS project and members of INFRAFRONTIER will participate in the working groups.

**ii Small molecule screening facilities**

During the Construction Phase of EATRIS small molecule screening facilities will be established or upgraded which allow the identification of potential drug targets and new chemical entities. Key aspects of the work during the preparatory phase will be the development of a concept for sharing and providing access to small molecule libraries among the users of EATRIS, the availability of professional expertise in the design of high throughput screens and relevant aspects of medicinal chemistry. A close interaction will take place with the biotech and pharmaceutical industry to define the transition of small molecule screening projects from the academic to the industrial sector.

**iii Imaging facilities**

Imaging facilities including MRI, PET and luminescence or fluorescence based imaging will be designed that allow state of the art analysis of molecular, cellular and pharmacological parameters important for the preclinical evaluation of new diagnostic or therapeutic strategies. Imaging facilities will need to be designed both for animal studies as well as for studies with human patients. A close interaction with the medical technology industry will take place to define the interface between the development of new imaging technology and the application of state of the art imaging technology as a validation tool. The responsible partner will be NEUROSPIN in Paris.

**iv Patient and population cohort access ports**

In this working group details for the integration of existing and future recruited patient and population cohorts will be worked out. A key aspect is the goal to use the strength of Europe's population in terms of genetic variation, critical mass, availability of founder populations etc. to establish an infrastructure (consisting of a combination of patient data and material) that is ideally suited to quickly test and validate preclinical concepts and move projects faster into later stages of clinical development. A close interaction will take place with both, the ESFRI BMS-BIOBANK and the BMS-ECRIN project to define the precise responsibilities with respect to ethical aspects, standardisation of patient sample preparation and archiving, data management, access policy, intellectual property rights, etc.

**v Bioprocess and GMP-facilities**

Biopharmaceutical GMP products can be manufactured at a few centralized facilities and not every translation centre or EATRIS partner needs to establish its own GMP facility. This is different from the requirements for cellular-biotherapeutic GMP, where close proximity of the GMP facility to patients and hospitals is important. A Europe wide survey will be carried out to

provide necessary information on the availability and capabilities of existing GMP facilities. A close interaction with industry will define the needs and possibilities of the academic and industrial partners. Special emphasis will be placed on the needs and requirements of academic and biotech companies for bioprocess development aspects (Pre-GMP) and on the support for translation researchers in terms of guidance and consultation with regulatory authorities. Close interaction and a joint working group is planned with the ECRIN-consortium, as ECRIN will take over responsibility for the biotherapeutic GMP infrastructure facilities in Europe. A number of SMEs also offers GMP-manufacturing. The key bottleneck however is a functioning highly integrated bioprocess-development, where academic researchers closely interact with biotechnology and regulatory experts to develop new manufacturing processes that are not yet routine in a drug development pipeline. This interface between academic bioprocess development and industrial GMP manufacturing opens up exciting opportunities for public private partnerships which will be explored during the preparatory phase of EATRIS.

**vi Facilities for Clinical Phase I studies**

EATRIS will provide facilities that allow Clinical phase I studies. These will be integrated in all EATRIS translation centres. In this working group a concept for having Clinical phase I studies very close to the basic research activities of the various translation centres will be refined and proposed. Very close interaction will take place with the ECRIN network, as this network will take over responsibility starting from Clinical Phase II. Members of EATRIS will join working groups from ECRIN and vice versa.

## *5. Further information, including strategic importance to ERA*

The European Technology Platform Innovative Medicine identified safety and efficacy of drugs as well as knowledge management and training in translational research as two of the major bottlenecks. They also pointed out that specific infrastructure for medical research is needed to create a research environment of high competitiveness in Europe. EATRIS is contributing to achieving this goal. It will support a European knowledge management sustained by a European network of interlinked medical translation centres. Training programmes are foreseen to overcome gaps in education for both, basic researchers and clinicians. Modern screening facilities will allow a targeted assessment and testing of new compounds. A strong user orientation in the offered services is a major goal of EATRIS. It will offer a research environment with a mutual exchange of different disciplines and will help to close the gap between basic and clinical research. This gap closing will be fundamental for increasing also technology development capacities in the corresponding fields.

The setting up of the EATRIS infrastructure will be a strategic investment to structuring the European Research Area by coordinating the existing national efforts in setting up translational research infrastructure. EATRIS will build on already existing centres of excellence in translational research. Translational research centres have shown to create clusters of excellence as the interaction of basic and clinical in medical research stimulates innovation. These clusters of excellence will be reinforced by the recognition as a European advanced translational research infrastructure in medicine and the extension of the infrastructure during the preparatory phase.

The service aspect is a crucial aspect to spread scientific excellence through Europe as a whole, as the advantages of the new infrastructure will not be limited to the clusters of excellence that are at the basis of the new infrastructure, but will be open to the whole of Europe. The services will be of special importance to researchers in those countries that are facing special challenges in terms of infrastructure, economic & institutional organisation such as convergence and outermost regions. European researches will be able to use the EATRIS infrastructure to move their research projects towards clinical application and thus capitalising on their research. The availability of this open infrastructure will substantially increase the attractiveness of the ERA for researchers as it increases their chances of exploiting their basic biomedical research projects.

However the services offered by EATRIS in the fields of training and consulting will able to reach even more European Researchers. By sensitising the European medical researchers e.g. to regulatory issues EATRIS will increase the number of basic research projects that have the potential for commercial application significantly and thereby generate a powerful European research force. This increase in academic research projects will strongly enhance the attractiveness of the European Research Area for the biomedical and pharmaceutical industry.

As the European Commission is launching a Joint Technology Initiative "Innovative Medicine Initiative (IMI)" to overcome the bottlenecks identified by the European Technology Platform in this field, EATRIS will form a complementary approach to support the overall goal of an accelerated discovery and development of more effective innovative medicines. A close interaction between EATRIS and IMI is envisaged as soon as the latter is formally established. As the IMI is strongly driven by the pharmaceutical industry, this will create a valuable link between academic to industrial research.

## *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 centres, clinical centres 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 centres 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 centres 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 Members*

| Scientific Partner | Funding Organisations (ministries, research councils) | Associated Partners |
|---|---|---|
| • Helmholtz-Zentrum fuer Infektionsforschung GmbH (HZI)<br>• Centre for Translational Molecular Medicine (CTMM)<br>• Commissariat a l`Energie Atomique (CEA)<br>• Imperial College School of Science Technology and Medicine<br>• Deutsches Krebsforschungszentrum (DKFZ)<br>• Universitetet i Oslo (UiO) | • Bundesministerium für Bildung und Forschung (BMBF)<br>• Niedersächsisches Ministerium für Wissenschaft und Kultur (MWK)<br>• Hermann von Helmholtz-Gemeinschaft Deutscher Forschungszentren e. V.<br>• The Netherlands Organisation of Health and Development (ZonMw)<br>• Medical Research Council (MRC)<br>• Swedish Research Council (SRC) | • Ministry of Education (Finland)<br>• Danish Agency for Science, Technology and Innovation<br>• Research Council of |

| | | |
|---|---|---|
| • Helsingin yliopisto (FIMM)<br>• University of Copenhagen, Cluster for Molecular Imaging (CMI)<br>• Karolinska Institutet (KI)<br>Instituto Superiore di Sanità (ISS) | • Stockholm County Council (SLL) | Norway |

## *8. Budgetary information*

| | | | |
|---|---|---|---|
| • *Preparatory cost*<br>• *6 Mio €*<br>• | • *Construction cost*<br>• *255 Mio € (+ 555 Mio € for phase 2 and 3.)*<br>• *estimation before start of preparatory phase* | • *Operation cost (total)*<br>• *50 Mio € / year*<br>• *estimation before start of preparatory phase* | • *Re- and decommissioning cost*<br>• *Not applicable*<br>• *estimation before start of preparatory phase* |

## *9. Timetable until operation*

| | | | |
|---|---|---|---|
| *Preparatory phase*<br>*3 years* | *Construction phase*<br>*2 years* | *Operation*<br>*20 years*<br>*(regular updates necessary)* | *Re- and De-commissioning*<br>*1 year* |

## *10. Contact*

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www.helmholtz-hzi.de

## *11. Progress in the preparatory phase*

The objective of the EATRIS Preparatory Phase will be to work out and reach consensus on a detailed plan for the construction and operation of a European infrastructure of translational research centres between the involved organisations (ministries, funding bodies and scientific institutions).

To reach this objective the following legal, governmental, financial, strategic and technical issues need to be addressed:

- A legal structure has to be chosen that is suitable for a distributed, pan-European research infrastructure with several partners from different countries. Within a dedicated

WP a legal framework will be developed to address legal issues to be solved before

the operation of the infrastructure like IPR agreements and contracts for users using legal consultancy. The governance structure will also be developed in this WP to en sure that the two structures are fitting. The governance structure has to be suited to support an efficient decision making process, enables the extension of EATRIS, en sures an efficient coordination of strategic activities with other ESFRI-BMS infrastruc tures and supports an effective day to day management.

- A financial management plan has to be established that includes developing a business plan for the construction and sustainable operation of EATRIS as well as financial controlling mechanisms. A dedicated WP will therefore include surveys on the costs for the construction and operation of the translational centres and evaluation of investment models and funding options as well as recruitment of additional sponsors. A key for a sustainable financial plan is the distribution of a multitude of funding agencies and ministries.

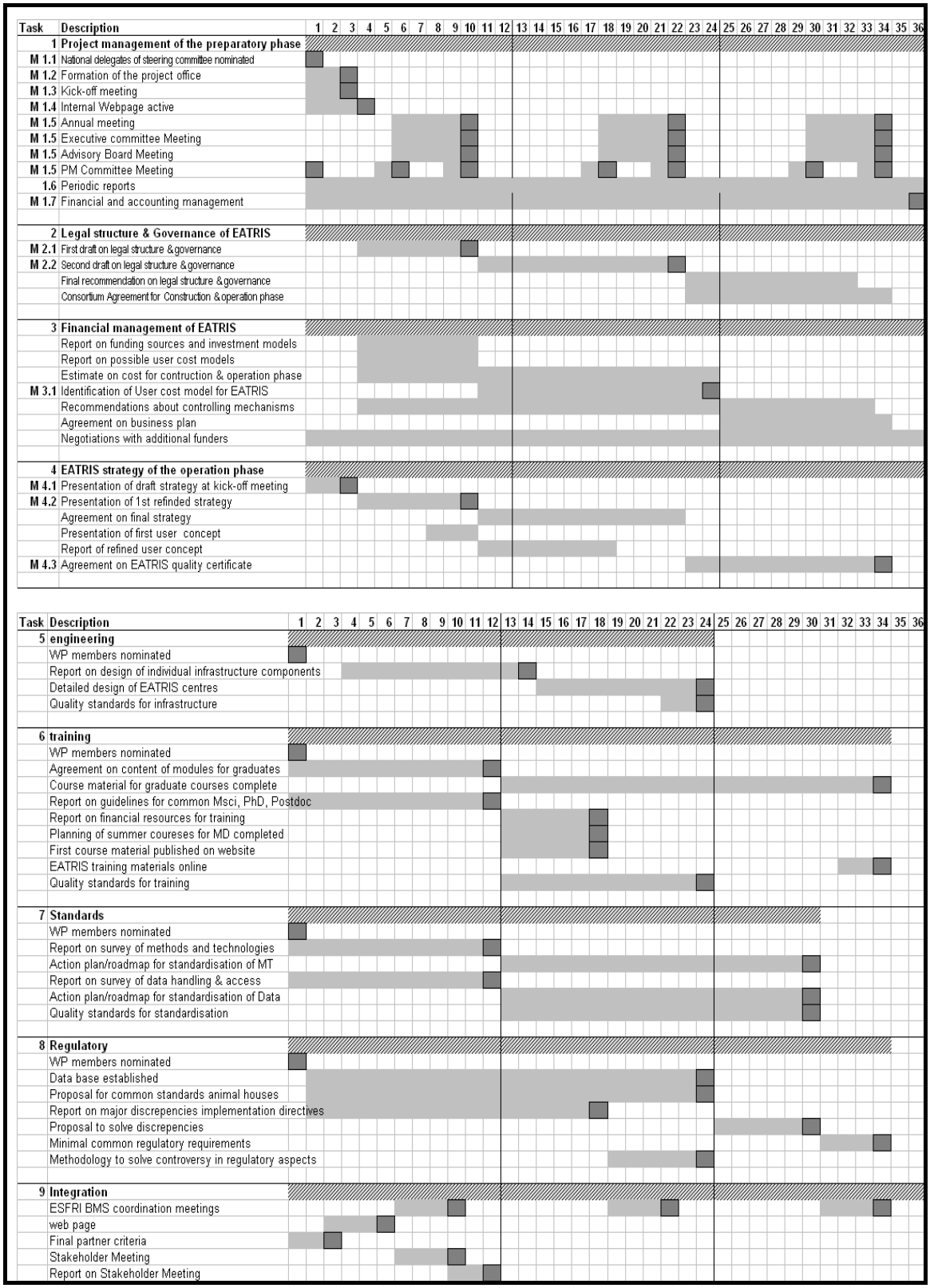
- A key issue that needs to be addressed during the Preparatory phase will be the refinement of the EATRIS strategy. The core of EATRIS will be a consortium of dedicated translational research centres across Europe, which will provide the infrastructure components necessary for translational research in order to overcome the bottlenecks in translational research. A WP is dedicated to refine the user strategy and define minimum standards for EATRIS translational centres. The activities of this WP will include stakeholder meetings and surveys.

- The detailed technical refinement of the infrastructure facilities needed to match the EATRIS user concept will be worked out.

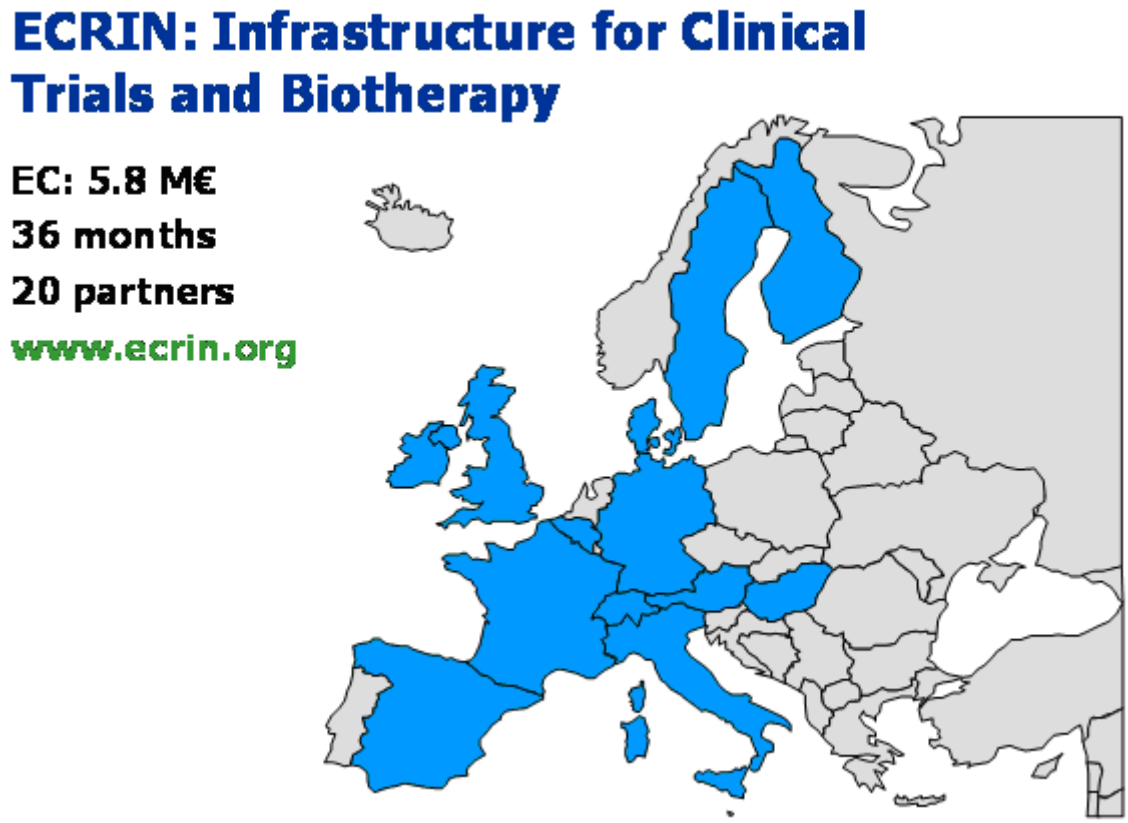
As the simple provision of access to translational infrastructure alone will not be sufficient to overcome all bottlenecks of translational research the EATRIS infrastructure will also need additional services. These are:

- Providing a training and education concept
- A concept for the harmonisation of translational methods and data handling
- Procedures to support researchers to comply with the regulatory requirements

In order to inform all relevant parties about the EATRIS activities, to coordinate EATRIS with other European initiatives and especially to drive the extension of EATRIS during the preparatory phase, there is a dedicated work package to include other countries into EATRIS. There will also be a central information gateway in form of a webpage. A joint coordination board with other EESFRI-BMS projects and the active recruitment of new members will contribute to the effective integration into the Europe Research Area.


Task
Description
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36
1 Project management of the preparatory phase
M 1.1 National delegates of steering committee nominated
M 1.2 Formation of the project office
M 1.3 Kick-off meeting
M 1.4 Internal Webpage active
M 1.5 Annual meeting
M 1.5 Executive committee Meeting
M 1.5 Advisory Board Meeting
M 1.5 PM Committee Meeting
1.6 Periodic reports
M 1.7 Financial and accounting management
2 Legal structure & Governance of EATRIS
M 2.1 First draft on legal structure &governance
M 2.2 Second draft on legal structure &governance
Final recommendation on legal structure &governance
Consortium Agreement for Construction &operation phase
3 Financial management of EATRIS
Report on funding sources and investment models
Report on possible user cost models
Estimate on cost for contruction & operation phase
M 3.1 Identification of User cost model for EATRIS
Recommendations about controlling mechanisms
Agreement on business plan
Negotiations with additional funders
4 EATRIS strategy of the operation phase
M 4.1 Presentation of draft strategy at kick-off meeting
M 4.2 Presentation of 1st refinded strategy
Agreement on final strategy
Presentation of first user concept
Report of refined user concept
M 4.3 Agreement on EATRIS quality certificate
Task
Description
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36
5 engineering
WP members nominated
Report on design of individual infrastructure components
Detailed design of EATRIS centres
Quality standards for infrastructure
6 training
WP members nominated
Agreement on content of modules for graduates
Course material for graduate courses complete
Report on guidelines for common Msci, PhD, Postdoc
Report on financial resources for training
Planning of summer coureses for MD completed
First course material published on website
EATRIS training materials online
Quality standards for training
7 Standards
WP members nominated
Report on survey of methods and technologies
Action plan/roadmap for standardisation of MT
Report on survey of data handling & access
Action plan/roadmap for standardisation of Data
Quality standards for standardisation
8 Regulatory
WP members nominated
Data base established
Proposal for common standards animal houses
Report on major discrepencies implementation directives
Proposal to solve discrepencies
Minimal common regulatory requirements
Methodology to solve controversy in regulatory aspects
9 Integration
ESFRI BMS coordination meetings
web page
Final partner criteria
Stakeholder Meeting
Report on Stakeholder Meeting

### 3.2.3 European Clinical Research Infrastructures Network (ECRIN)




The ECRIN consortium organised a pre-kickoff meeting in Milan on 27 February and invited its members to its first official kick-off meeting, which was held on 20 May in Brussels.

During the previous two years, ECRIN participated in the FP6 Pharmatech Platform project to contribute to the Innovative Medicines Initiatives (IMI) Strategic Research Agenda. The consortium also received a FP6 funding (health priority) to identify the bottlenecks of multinational collaboration (ECRIN-RKP, 2004-2005), subsequently followed by a second funding (FP6, health priority) to write a set of procedures and guidelines to be used for multinational clinical studies (ECRIN-TWG, 2006-2008). ECRIN also won FP7 funding (health priority) to provide metrics on the impact of the 2001/20/EC Directive on multinational clinical trials (ICREL, 2007-2008) and contributed to the disease-oriented networks (FP7, health priority-funded ENBREC project on mood disorders, 2008-2010).

Currently ECRIN plans to increase the number of partners especially from Eastern European Countries. This requires the set up of a national coordination for clinical research, with the help of the Capacity Building workpackage.

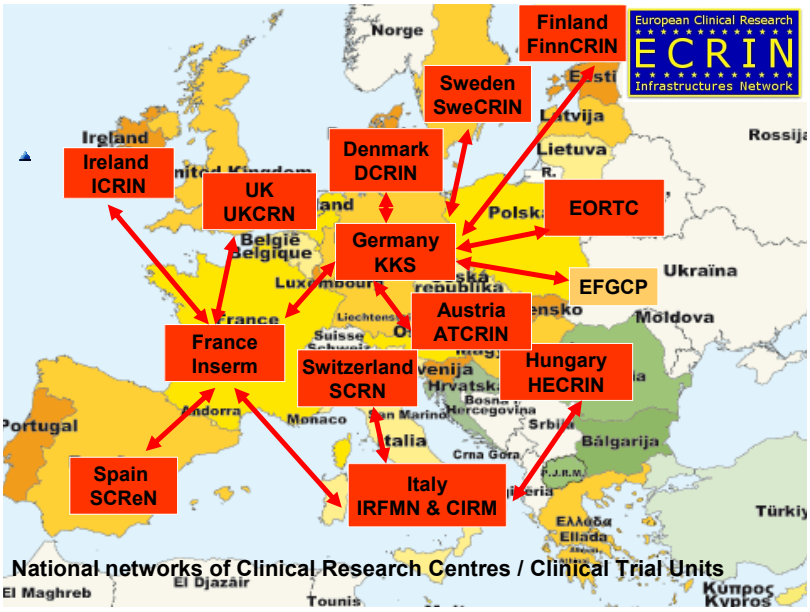
| *1. Name and descriptive title* |
| --- |
| **ECRIN:**<br>**European Clinical Research Infrastructures Network and biotherapy facilities** |

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

ECRIN (European Clinical Research Infrastructures Network, www.ecrin.org) is designed to bridge the fragmentation of clinical research in Europe through the connection of national networks of clinical research centres and clinical trial units. Participants are currently Austria, Denmark, Finland, France, Germany, Hungary, Ireland, Italy, Spain, Sweden, Switzerland, the United Kingdom, and the EORTC. It will provide integrated, 'one-stop shop' services to investigators and sponsors in multinational studies (patient recruitment and investigation, data management, GMP manufacturing of biotherapy products, quality assurance, monitoring, interaction with ethics committees and regulatory authorities, and adverse event reporting).

**Users** will be investigators and sponsors in the academic and SME sector.

**Participants** are the **national coordination** of clinical research infrastructures, and national **ministries and funding agencies** in order to reach an agreement ensuring the long-term sustainability of the infrastructure.




## 3. Science case

Fragmentation of health and legislative systems in the EU hampers the competitiveness of its clinical research. European clinical research needs an efficient, integrated, and professionalised infrastructure, based on competence centres able to provide efficient support through a consistent set of services for clinical trials: patient recruitment and investigation, data management, GMP manufacturing of biotherapy products, quality assurance, monitoring, ethics, regulatory affairs and adverse event reporting. This integrated, EU-wide infrastructure will allow the conduct of multinational trials in Europe, taking advantage of the EU population and competencies, unlocking latent expertise, and combining and connecting patients currently scattered across the EU member states.

ECRIN is designed to bridge the fragmentation of clinical research in Europe through the interconnection of national networks of clinical research centres and clinical trial units. ECRIN plans extension to national infrastructure networks in other member states, and stimulates the set-up of new national networks able to provide support to clinical research in any medical field for further connection to ECRIN. Therefore this integrated clinical research infrastructure, unique in the EU, will provide support to any type of clinical research, and in any medical field.

A first (ECRIN-RKP) FP6-funded step helped identify bottlenecks to multinational co-operation, highlighting the poor capacity of public institutions to act as a sponsor in multinational studies. In the ongoing second FP6-funded ECRIN step (ECRIN-TWG), transnational working groups are in charge of defining procedures and guidelines for multinational trials in the EU. Six working groups respectively focus on ethics, regulation, adverse event reporting, data management, monitoring, quality assurance, and another is designed to translate this knowledge into a training programme. This is achieved through the local contribution of ECRIN correspondents embedded in each national co-ordination. The objective is to prepare the network to provide integrated, 'one-stop shop' services to investigators and sponsors in multinational studies.

## *4. The Concept case*

ECRIN-PPI consists of building an EU-wide infrastructure for clinical trials and biotherapy. This requires **services** whose main objective is to relay the sponsor's tasks and to support investigation in other countries. World-class services will be provided to users through a network implementing harmonised practice and SOPs, with staff trained to multinational studies, and with high quality infrastructures, data centres and GMP facilities:

1 - support to the interaction with ethics committees
2 - support to the interaction with competent authorities and in regulatory affairs
3 - support to adverse event reporting
4 - support to drug dispensing
5 - support to the circulation of blood and tissue samples
6 - support to study monitoring
7 - data management
8 - GMP manufacturing of biotherapy products
9 - patients recruitment and investigation.

In addition, consulting will be provided to investigators and sponsors before the clinical trial (including on regulation and ethics, centre selection, cost evaluation, funding opportunities, insurance).

**Users** will be investigators and sponsors in both the academic and industry sector, and services provided by this infrastructure are particularly relevant for research on rare diseases, for academic clinical research institutions, and for clinical trials steered by biotechnology SMEs who often lack the capacity to manufacture biotherapy products and to act as a sponsor in the conduct of EU-wide studies. Hereby ECRIN will stimulate EU research on prevention, diagnosis and treatment, hence improving healthcare delivery to patients and citizens.

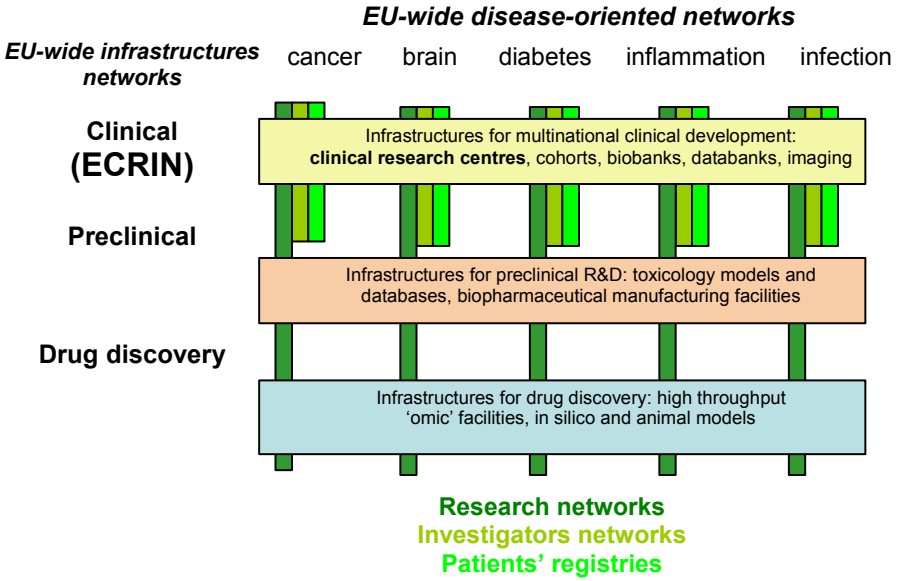
Building this EU-wide infrastructure will have a structuring effect by the harmonization of tools, of SOPs, of practice, of training of personnel. It will help the users of the infrastructure (academic researchers and investigators, disease-oriented scientific networks, EU networks of excellence and related collaborative projects, and public-private partnership projects (including the FP7 Innovative Medicines Initiative (IMI) projects) to prepare and conduct multinational clinical studies in the EU. This integrated EU infrastructure for multinational studies will provide users with a one-stop shop access to the EU patient population, and unlock latent scientific potential.

## *5. Further information, including strategic importance to ERA*

Through the **integration and harmonisation** of national clinical research capacities, ECRIN will affect the scientific competitiveness of Europe in biomedical research, providing access to competence centres conducting clinical studies with high quality standards, and facilitating multinational academic clinical studies, enlarging the capacity for patients' enrolment.

This will have a particular impact on translational research, allowing to best exploit the out-

comes of experimental research, and in strategy studies translating clinical research into healthcare. These services are critical for or public research institutions, whose role as a single sponsor in multinational studies is made increasingly complex due to the implementation of the 2001/20/EC Directive on Clinical Trials. Industry and small and medium-sized enterprises (eg, biotechnology and medical-device companies) will also benefit from these services.
ECRIN will have a long-term **structuring effects** on national clinical research infrastructures and funding, both in countries connected and in countries not yet connected, through its capacity building work package. ECRIN will also structure the development of GMP manufacturing facilities and data centres at the EU level. It will also prepare an **ERA-net** on clinical research, allowing to fund multinational projects.
ECRIN participates in discussions on **European regulation** on clinical research and, based on its multinational vision, makes proposals for an improvement and a better harmonisation of the current legislative framework.




ECRIN will participate in the long-term **structuring of specialty or disease-oriented networks**. It will also play (together with the other ESFRI-BMS research infrastructures) a critical role in the implementation of the **Innovative Medicines Initiative** (IMI) strategic research agenda (SRA), as the availability and quality of relevant research infrastructures are critical to the attractiveness for public-private partnership projects.

Through the joint strategic board, close collaboration will be established with the **other EFSRI-BMS** infrastructure projects, particularly the BBMRI (Biobanks) and EATRIS (translational research) projects in order to develop synergies and avoid duplication. Fostering such collaboration will provide users with a wide range of integrated services for preclinical, clinical and biomarker development.

## *6. Identification of other socio-economic impacts*

Impact on **health**: studies on rare disease will take advantage of the EU population, allowing the EU to improve their diagnostics and treatment. In addition, large-scale clinical studies are necessary to improve diagnostic and treatment strategies, and to translate into healthcare the outcome of innovation.

Impact on EU **economy**: facilitating multinational clinical trials in the EU will have an impact on the pharmaceutical industry during the drug development process and in various pubic private partnership programmes, including research on biomarkers as mentioned in the IMI SRA. It will benefit the biotechnology and medical device SMEs who often lack the capacity to act as a

sponsor in the EU, facilitating their multinational trials in the EU. It will also facilitate the clinical proof of concept for projects arising from academic institutions, hence the transfer from public research to the spin-off companies or SMEs.

ECRIN will also impact on **citizens, patients, and patients associations** through its education and communication policy on clinical research. ECRIN promotes transparency, patients' rights and safety, spreading the best practice across the EU, and organise on May 20th an annual communication event targeting patients and citizens, the International Clinical Trials Day.

***7. Participating Members***

| Scientific Partners | Funding Organisations (ministries, research councils) | Associated Partners |
|---|---|---|
| INSERM, France<br>Heinrich Heine Universitaet Duesseldorf, Germany<br>Consorzio Italiano per la Ricerca in Medicina, Italy<br>Rigshospitalet Copenhagen, Denmark<br>Istituto Mario Negri, Italy<br>Hospital Clinic i Provincial Barcelona, Spain<br>Karolinska University Hospital, Sweden<br>Medical Research Council, Hungary<br>Dublin Molecular Medicine Centre, Ireland<br>University of Leeds, UK<br>EORTC, Belgium<br>Medical University of Vienna, Austria<br>Universitat Bern, Switzerland<br>Technology Centre Teknia, Finland | Bundesministerium für Bildung und Forschung, Germany<br>Health Research Board, Ireland<br>Spanish Medicines Agency and Medical Devices, Spain<br>Instituto de Salud Carlos III, Spain<br>Medical Research Council, UK<br>Istituto Superiore di Sanita, Italy | EFGCP, Belgium,<br>Telematikplattform, Germany<br>Ministère de la Recherche, France<br>Ministère de la Santé, France<br>Agency for Science, Technology and Innovation, Denmark<br>Science Foundation of Ireland, Department of Health, UK<br>Ministry of social affairs and health, Finland<br>Bundesministerium für Wissenschaft und Forschung, Austria<br>Vinnova, Sweden<br>Ministerio de Educacion y Ciencia, Spain<br>Federal Science Policy Office, Belgium<br>TEKES, Finland |

***8. Budgetary information***

| Preparatory cost: | Construction cost: | Operation cost: | Re- and decommissioning cost |
|---|---|---|---|
| 7 Mio € | up to 50 Mio € (data centres, biotherapy centres and GMP facilities) | 5 Mio € / year (EU correspondents, coordination, datacentres, GMP facilities) | (total in Mio €): NA |

***9. Timetable until operation***

Activation of work packages during the preparatory phase will be progressive, as the infra-

structure will be able to provide increasingly integrated support to clinical trials during this period, resulting in a gradual transition from the preparatory to the operation phase, as partial support to pilot projects will be possible at the end of the first year of the preparatory phase.

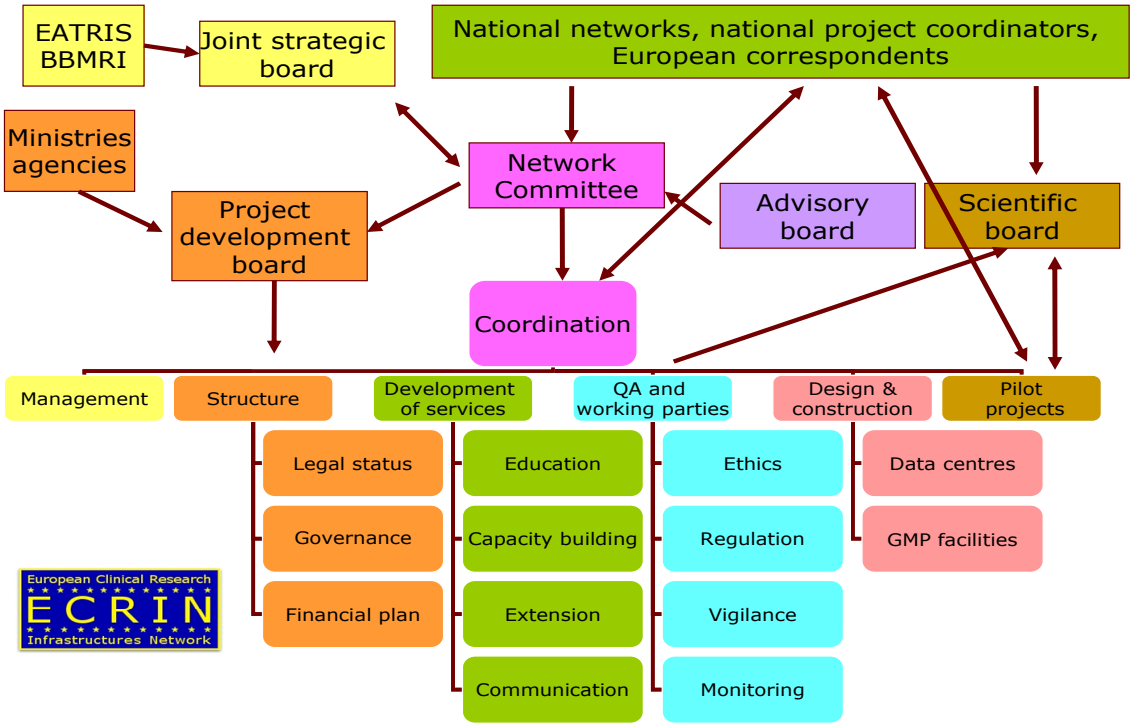
| Preparatory phase 2008-2011 | Construction phase 2011-2014 | Operation From 2014 | Re- and Decommissioning |
|---|---|---|---|

## *10. Contact*

Project coordinator: Jacques Demotes-Mainard
INSERM – DRCT, 101 rue de Tolbiac, room 1425, 75654 PARIS cedex 13
demotes@tolbiac.inserm.fr, tel +33 1 44 23 62 85
www.ecrin.org

## *11. Progress in the preparatory phase*

The preparatory phase of the infrastructure for clinical trials and biotherapy will transform a network, sharing tools and practice, into an operating EU institution with financial sustainability, providing high-quality services to multinational clinical research, and prepare the construction of data centres and of GMP facilities. The construction step will merely concern the data centres and the GMP manufacturing facilities for biotherapy, according to their specification and planning performed during the preparatory phase.




As a result, the preparation phase covers:

WP2: Selection of a ***legal status*** allowing contracts with sponsors, efficient financial management within the network, extension to new member states, and adaptation of the ***governance*** structure allowing efficient decision-making regarding the access of users to the in-

frastructure, the financial plan for the construction and operation phase, and the strategic co-operation with other ESFRI-BMS infrastructures.

WP3: Agreement on a ***financial plan*** leading to a long-term sustainability. This will require surveys on the current funding to, and on construction and operation costs and revenues of clinical research infrastructures. Funding of the ***construction step*** should be based on the support from the Capacity Programme, from member states, the EU structural funds, investment of industry partners, and self-financing; and for the ***operation phase,*** mainly on EU funding to the operation of integrated infrastructures, on operation revenues and on the support of member states to their national infrastructure.

WP4: Survey, performed jointly with the EATRIS project, on needs and existing resources in terms of ***GMP facilities*** (biopharmaceuticals, biotherapy), then design and planning, in co-ordination with EATRIS, of the construction of such GMP facilities.

WP5: an ***education programme*** to train the personnel within national networks to multinational clinical studies, with the support of train-the-trainers summer schools and of e-learning tools.

WP6: the ***extension*** to other EU member states (or to other EU-wide infrastructures) will be planned according to defined criteria, and the setup of national network will be stimulated.

WP7: A ***capacity building*** programme will help strengthening the capacity of national co-ordination to perform sponsor's tasks in EU-wide studies.

WP8: the ***quality assurance*** system will play a critical role in the project. Standard operating procedures (SOPs) and guidelines for multinational studies will be constantly updated through the activity of the corresponding working groups (ethics, regulation, vigilance, monitoring), some of these activities being shared with the EATRIS and the BBMRI projects. In addition, the quality assurance system will be upgraded, as national centres and network will be demanded to fulfil QA requirements to ensure the high quality of services.

WP9: Various tools will promote ***internal communication*** within the network, and ***external communication*** with users of the infrastructure, with patients, and with citizens. A major event will be the annual ECRIN meeting.

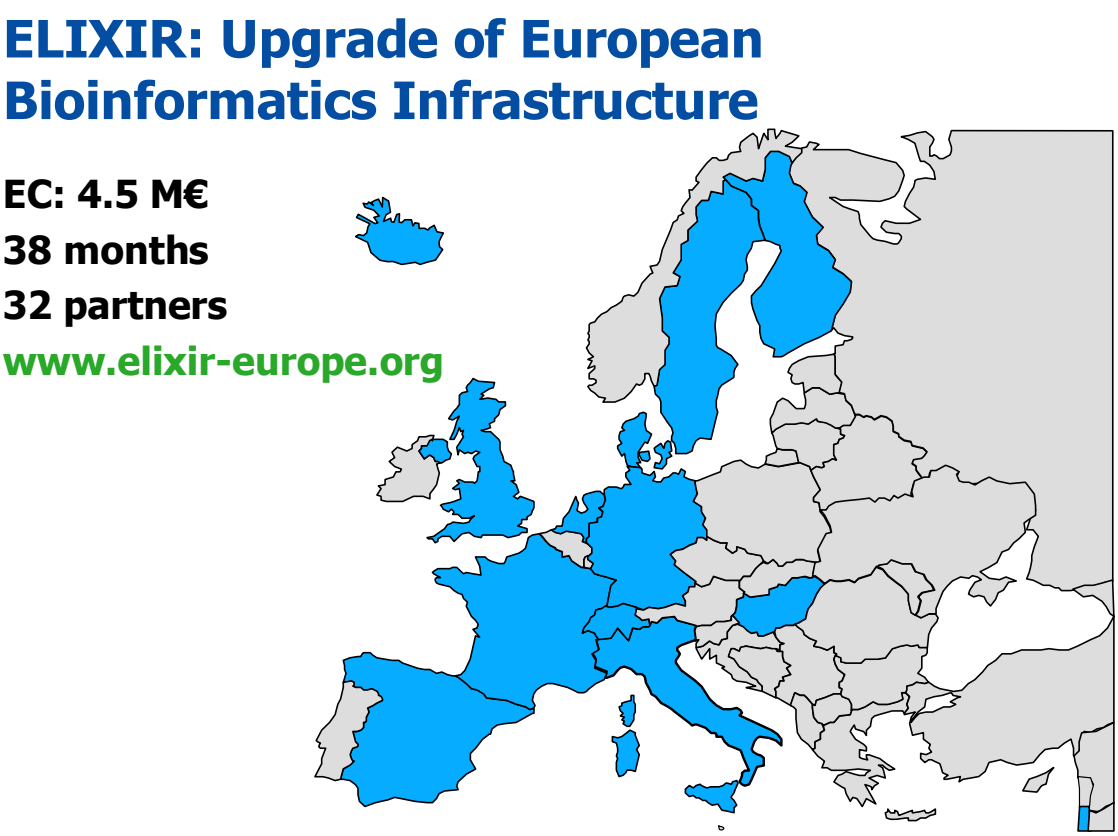
WP10: Specifications on the requirements for ECRIN ***data centres*** will be prepared, then implemented through a first call for accreditation of a prototype data centre.

WP11: Support to ***pilot projects*** evaluated by the scientific board, corresponding to various types of clinical studies will be necessary to assess the validity of the overall organisation and of the quality assurance system, and to refine the cost evaluation.

| | M 3 | M 6 | M 9 | M 12 | M 15 | M 18 | M 21 | M 24 | M 27 | M 30 | M 33 | M 36 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **WP1. Management** | | | | | | | | | | | | |
| Management of the grant agreement | | | | | | | | | | | | |
| Management of the overall strategy | | | | | | | | | | | | |
| **WP2. Legal status and governance** | | | | | | | | | | | | |
| Agreement on the governance | | | | | | | | | | | | |
| Implementation of the governance | | | | | | | | | | | | |
| Agreement on legal status | | | | | | | | | | | | |
| Implementation of status | | | | | | | | | | | | |
| **WP3. Financial plan** | | | | | | | | | | | | |
| Surveys | | | | | | | | | | | | |
| Evaluation of the costs | | | | | | | | | | | | |

| | M 3 | M 6 | M 9 | M 12 | M 15 | M 18 | M 21 | M 24 | M 27 | M 30 | M 33 | M 36 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Contract on the business plan | | | | | | | | | ■ | ■ | ■ | ■ |
| **WP4. GMP facilities for biotherapy** | | | | | | | | | | | | |
| Surveys | ■ | ■ | ■ | ■ | | | | | | | | |
| Plan for construction and design | | | | | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ |
| **WP5. Education and training** | | | | | | | | | | | | |
| e-training tool | ■ | ■ | ■ | ■ | ■ | ■ | | | | | | |
| Summer school | | ■ | | | | ■ | | | | ■ | | |
| Training sessions | | | | ■ | | | | ■ | | | | ■ |
| **WP 6 Extension** | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ |
| **WP7 Capacity building** | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ |
| **WP8 Quality Assurance** | | | | | | | | | | | | |
| Update of the existing system | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ |
| QA specifications | ■ | ■ | ■ | ■ | | | | | | | | |
| Implementation at national level | | | | | ■ | ■ | ■ | ■ | | | | |
| Audit strategy and cost evaluation | | | | | ■ | ■ | ■ | ■ | | | | |
| **WP 9 Communication** | | | | | | | | | | | | |
| Internal and external communication | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ |
| ECRIN meeting | ■ | | | | ■ | | | | ■ | | | |
| **WP10 Data Centres** | | | | | | | | | | | | |
| Specifications for data centres | ■ | ■ | | | | | | | | | | |
| Development of a prototype | | | ■ | ■ | ■ | ■ | ■ | ■ | | | | |
| Evaluation of cost, plan for construction | | | | | | | | | ■ | ■ | ■ | ■ |
| **WP11 Pilot projects** | | | | | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ |

### 3.2.4 Upgrade of European Bioinformatics Infrastructure (ELIXIR)




ELIXIR will permit the integration and interoperability of diverse, heterogeneous, potentially redundant information that is essential to generate and utilise biological 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 and user-friendly portal for users. It will manage the European component of the major international collaborations that collect, curate and annotate biological information world-wide. It will develop processes for (i) managing the integration of novel data-types, (ii) supporting for interoperability of analytical tools (although it will not support the development of the tools themselves, except in the very limited case where the tools are necessary for the ELIXIR core mission) and (iii) developing standards and ontologies for biological information. ELIXIR will support the other ESFI Biological RI projects by providing them with access to the molecular sequence, structure and related information that they will need to construct their infrastructures.

The ELIXIR consortium consists of 32 organisations, including 2 ministries, 14 funding organizations and 16 associated scientific organizations from 13 European countries. The proposal was accepted by the European Commission and awarded 4.5 Mill Euro funding for a 38 months preparatory phase. The output of the preparatory phase will be Memoranda of Understanding between the participating organisations to construct the Research Infrastructure. The starting date of ELIXIR was November 2007. The ELIXIR Project Manager (andrew.lyall@ebi.ac.uk) and ELIXIR Logistics Administrator (holly.edwards@ebi.ac.uk) have been appointed. The first two meeting of the Steering Committee were held in Hinxton, Cambridge on the 28 to the 29 January 2008 and on the 9 April 2008 respectively.

ELIXIR has the largest user community of any of the ESFRI Research Infrastructures, potentially many millions. For this reason, consultation with the user community (Bioinformatics Communities, Industry, Data providers and

Rest of the World) is a major activity leading to currently run two European surveys, for data-users and data-providers.

ELIXIR is organised into 14 Work Packages and nearly 20 Committees. Most of the committees have been constituted and have met for the first time. They will all be giving update presentations at the Steering Committee and are scheduled to present draft final reports at the next Stakeholders Meeting. A Wiki has been created at EMBL-EBI for the Work Package and Committee members that will be used to develop the final reports and to manage the discussions necessary to achieve this.

The first Stakeholders meeting was held in Hinxton on 10 April 2008 and there were 143 registered from 27 countries. All of the work packages gave current status presentations at this meeting. These presentations have been placed on the ELIXIR website with unrestricted access. The Stakeholders Meeting was structured so as to allow as much intervention and interaction with and between the attendees. There were several lively sessions involving all of the attendees. Feedback was collected from these sessions. This is currently being processed and will be used to inform the next Stakeholders meeting which is to be held on 18 November 2008 at Hinxton. A report of the first stakeholder meeting is in preparation.

Four members of the ELIXIR team are also member of INSTRUCT.ELIXIR and INSTRUCT have identified seven areas of activity where they can co-operate. These are (i) Software development, (ii) Data validation, (iii) Structure generation, (iv) Structural biology research, (v) Molecular modelling, (vi) Users of structural biology knowledge and (vii) Electron microscopy. Over the coming months ELIXIR will identify similar areas of activity where it can co-operate with BBMRI, INFRAFRONTIER, EATRIS and ECRIN. The ELIXIR PM will be attending many meeting to work these out.

***1. Name and descriptive title***

**ELIXIR: European Life-science Infrastructure for Biological Information**

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

The objective of the ELIXIR preparatory phase is to produce a memorandum or memoranda of understanding between organisations (government agencies, research councils, funding bodies and scientific organisations) within the member states, with the purpose of constructing a world class and globally positioned European infrastructure for the management and integration of information in the life sciences.

To achieve this, we will address the following tasks and issues:
1 Define the scope of the infrastructure, its role and benefits
2 Define an appropriate governance and legal structure
3 Define a long term funding structure to provide a sustainable infrastructure
4 Define the requirements for the European Data Centre in the next 5-10 years and make plans to meet these needs
5 Involve all relevant stakeholders, including users, data providers, and tools providers to ensure that the infrastructure meets their needs
6 Explore integration and interoperability between core and specialised data resources and the development of standards in newly emerging fields
7 Define the critical interdisciplinary links that need to be forged between the 'biological' and related scientific disciplines, including medicine, agriculture and the environment
8 Define the needs of related European industries
9 Define a training strategy to ensure that Europe effectively exploits all the available information

The specific activities of the preparatory phase will include:
A Holding stakeholder meetings to bring together national representatives, key scientific opin-

ion and funding organisations.
B Establishing working parties, supported by technical feasibility studies where appropriate, to address the tasks and issues above with final reports at month 20.
C Consolidating these reports into a management and funding proposal to be sent to member states and funding agencies with draft MoU by month 26 to seek agreement by month 38.

## *3. Science case*

A European infrastructure for Biological Information is needed because:

- Optimal exploitation of life-science data is crucial to research
- The exploitation of the flood of data promises substantial and diverse increments in well-being.
- Huge investment in science will be wasted if its output is not preserved.
- Public databases are the only way to satisfy scientific needs
- Current European funding is inadequate.
- A unified European funding strategy is essential to minimise costs
- Information infrastructure costs are a small fraction of the data gathering costs
- Coordination of standards is essential to realise the composite value of the data.
- Data collections are growing exponentially
- New high-throughput methods generate new data requirements
- A single European voice will influence global decisions and maintain open access
- Significant upgrades are essential to provide uninterrupted robust services
- The already-huge user community is growing relentlessly
- New accession states are emerging as strong contributors to and users of the information

These challenges need to be addressed at a European (rather than national) level because the benefits are pan-European, there is a need for European coordination and it is important for European competitiveness and return on investment.

## *4. The Concept case*

The mission of this European Life Sciences Information Infrastructure is to construct and operate a sustainable infrastructure for biological information in Europe to support life science research and its translation to medicine and the environment, the bio-industries and society. This will enhance all research and industry associated with living systems including: health and medicine, the environment, the bio-industries and society.

To achieve this we will

- Establish a trans-national infrastructure for biological information and service providers, including existing national infrastructures and networks.
- Implement a major upgrade to the current infrastructure for the core molecular information at the European Bioinformatics Institute (EMBL-EBI), including construction of a European Biomolecular Data Centre.
- Promote the use of state-of-the-art IT technology for data integration and database interoperability
- Promote and further develop the use of distributed annotation technologies for large scale European collaborations in the life science databases.
- Promote the development of infrastructures for biological information in the new accession states.
- Develop an appropriate legal and financial framework for the construction and sustainable operation of this infrastructure.
- Promote the formation of an associated European framework for Training and Outreach.

This will contribute to European science by:

- Optimising access and exploitation of shared life-science data.
- Ensuring longevity of the data and protecting investments already made in research which collected the data.
- Increasing the competence and size of the already-large user community by strengthening national efforts in training and outreach.
- Enhancing the effectiveness of pan-European collaboration by improved data exchange.
- Enhancing the global success and influence of Europe in life science research and industry.

ELIXIR will comprise:

- An interlinked collection of 'core' and specialised biological data resources and literature.
- Standards and ontologies for newly emerging data.
- A major upgrade for the core information resources at the EBI.
- New data resources as appropriate.
- Integration and interoperability of diverse heterogeneous data.
- Rapid search and access through friendly portal(s) supported by appropriate computer hardware infrastructure.
- Infrastructure linking core data resources and national bioinformatics data and service providers.
- Infrastructure to enable Distributed Annotations and Tool Development.
- The opportunity to establish infrastructures for life science information in the accession states.
- Links between molecular resources and developing resources for medicine (e.g. biobanks), agriculture and the environment (e.g. biodiversity).
- Access to high performance computing, through links to Europe's Supercomputer Centres.
- Coordination and Provision of Training and Outreach across Europe to enhance national efforts.
- Strong links to European bio-industries to ensure the optimal translation of life science research into the bio-industrial sector in Europe.

EMBL funding supports part of the core EBI data resources, including DNA sequences, genome sequences, protein sequences, protein structures, expression data, tools for accessing, analysing and integrating data. Current EMBL support does not include funding for new data resources (e.g. chemicals in biology & medicine (metabolites, pharmaceuticals), imaging data (from cells to organisms), human variation data, Ensembl for non-vertebrates, a major literature resource. Also there is little national funding for distributed specialist resources and for the hardware, software and personnel to integrate the specialist distributed resources with core resources. These latter areas will be considered and included in the ESFRI ELIXIR pan-European infrastructure.

The Preparatory Phase of ELIXIR will define the most appropriate structure for the infrastructure. There can be no definitive statement of priorities or selection at this time since this would be based on considerations made without resolution of legal, governance, strategic and financial issues.

### *5. Further information, including strategic importance to ERA*

The anticipated impact of ELIXIR is that it will contribute technological development capacity in the European Research Area in the following ways:

- Basic world-class infrastructure to support world-class research

- Facilitate exploitation of public data
- Facilitate integration of data
- Ensure coordinated approach to establishment and support of core data resources, avoiding duplication of effort and resources
- Provide support for life science industries, to ensure that they are able to fully exploit available knowledge and so boost the knowledge economy
- Encourage the spread of excellence in computational biology throughout Europe, from the convergence regions to the outermost regions – with computational networks, this is now entirely possible.
- Provide a coordinated training strategy across Europe to ensure all our life scientists know how to exploit available data.
- Provide a single voice for Europe in global infrastructure consortia and decisions.
- Provide an effective training strategy for life scientists

## *6. Identification of other socio-economic impacts*

At a general level, the catalytic effect of this project will result in pan-European impact, will benefit from the participation of multiple centres and multiple member state organisations, is important for European scientific competitiveness and cannot reasonably be expected to be funded by a single member state.

- The infrastructure will capitalise on existing funding across Europe: Currently the member states already invest considerable sums into collecting data and bioinformatics research. It is now generally acknowledged that the data and information generated by such research must be efficiently captured electronically and made available. A Europe-wide approach to this problem will make the whole process more cost-effective and much synergy will de generated by the integration of information across Europe.

The infrastructure builds strongly on past and current EU consortia, including networks of excellence and integrated projects. The infrastructure proposed in ELIXIR will complement (not replace) these research projects. Indeed we envisage this infrastructure supporting an extended portfolio of EC-supported and member-state supported research projects and consortia.

## *7. Participating Members*

| Scientific Partner | Funding Organisation |
|---|---|
| The Barcelona Supercomputing Centre | The UK Biotechnology and Biological Sciences Research Council |
| The Spanish National Cancer Research Centre | The German Federal Ministry of Education and Research |
| The Center for Advanced Studies, Research and Development in Sardinia | The Italian National Research Council Department of Life Sciences |
| The Finnish IT center for science | The German Research Foundation |
| The Center for Biological Sequence Analysis at The Danish Technical University | Genome Espana |
| Erasmus Medical Center | The French National Institute for Research in Computer Science and Control |
| EMBL-EBI | Israel Ministry of Science & Technology |
| The German Research Centre for Environmental Health | UK Medical Research Council |
| The Hungarian Institute of Enzymology | UK National Environment Research Council |
| Linköping University Department of Physics, Chemistry and Biology | The Netherlands Organisation for Scientific Research |
| Radboud University Nijmegen Medical Centre | Icelandic Center for Research |
| The Sanger Center | Sardenga Ricerche |
| | The Swedish Research Council |
| | The Wellcome Trust |

| | |
|---|---|
| The Swiss Institute of Bioinformatics<br>Syngenta<br>The Technical University of Braunschweig<br>The University of Bordeau 2 | The French National Institute for Agricultural Research<br>The French National Institute for Health and Medical Research |

***8. Budgetary information***

| | | | |
|---|---|---|---|
| Preparatory cost<br>4.5 Mio € | Construction cost (total in Mio €)<br>470 Mio € to be further determined in pp | Operation cost (total)<br>100 Mio € to be further determined in pp | Re- and decommissioning cost (total in Mio €) |

***9. Timetable until operation***

| | | | |
|---|---|---|---|
| Preparatory phase<br>2007 to 2010 | Construction phase<br>2011 | Operation<br>2012 onward | Re- and Decommissioning |

***10. Contact***

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***11. Progress in the preparatory phase***

The starting date of ELIXIR was November 2007. The ELIXIR Project Manager (andrew.lyall@ebi.ac.uk) and ELIXIR Logistics Administrator (holly.edwards@ebi.ac.uk) have both been appointed. The first two meetings of the Steering Committee were held in Hinxton, Cambridge on the 28 to the 29 January 2008 and on the 9 April 2008 respectively.

ELIXIR probably has the largest user community of any of the ESFRI Research Infrastructures, potentially many millions. (For example, EMBL-EBI currently performs analyses for more than 1 Million unique users per annum). For this reason, consultation with the user community is a major activity. WP3 (Users) has four committees that manage this (Bioinformatics Communities, Industry, Data providers and Rest of the World). In addition it is running two European surveys, for data-users and data-providers. These have been developed and are currently being tested in a pilot-phase. We plan to launch them before the summer vacation.

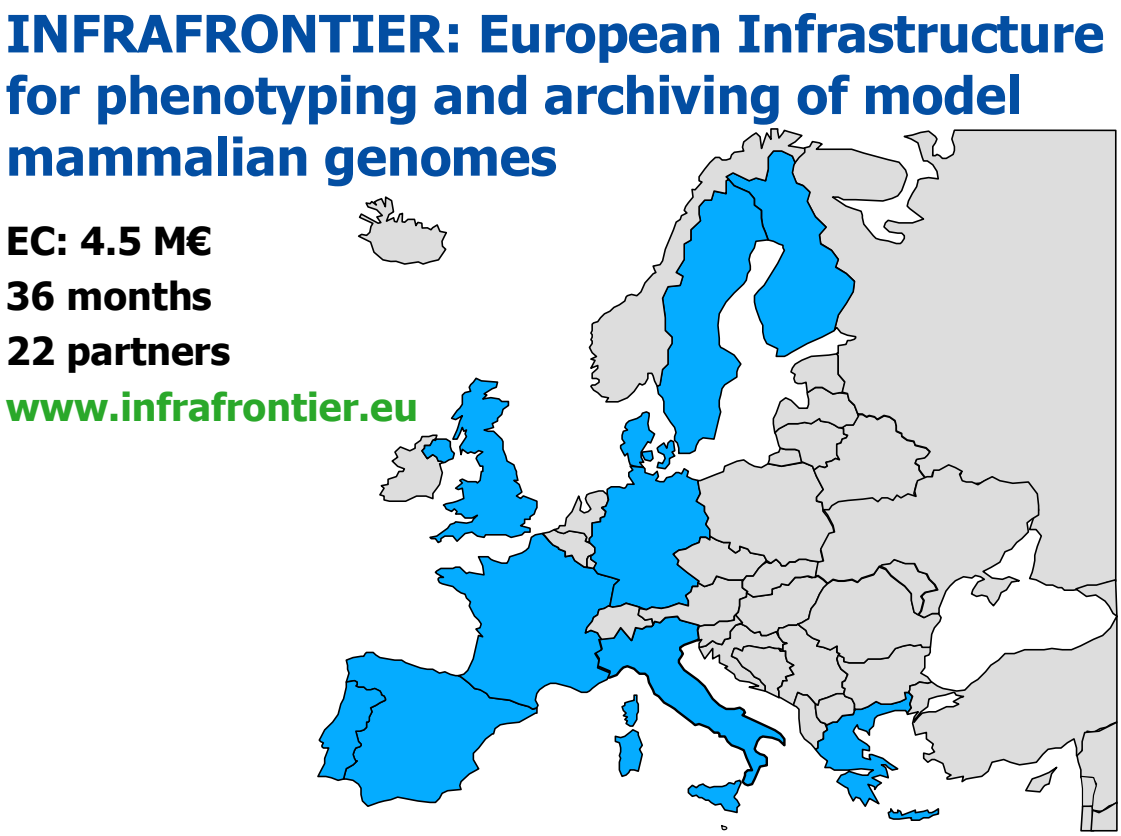
The first Stakeholders meeting was held in Hinxton on 10 April 2008 and was attended by 143 people from 27 countries. All of the work packages gave current status presentations at this meeting. These presentations have been placed on the ELIXIR website with unrestricted access. The Stakeholders Meeting was structured so as to allow as much intervention and interaction with and between the attendees. There were several lively sessions involving all of the attendees. Feedback was collected from these sessions. This is currently being processed and will be used to inform the next Stakeholders meeting which is to be held on 18 November 2008 at Hinxton. All are welcome to attend this meeting. A report of the first stakeholder meeting is in preparation.

ELIXIR is organised into 14 Work Packages and nearly 20 Committees. Almost all of the committees have been constituted and have met for the first time. They will all be giving update presentations at the next Steering Committee in September and are scheduled to present draft final reports at the next Stakeholders Meeting. A Wiki has been created at EMBL-EBI for the Work Package and Committee members that will be used to develop the final reports and to

manage the discussions necessary to achieve this.

It is envisaged that Elixir will provide support to the other ESFRI BMS projects as well as ESRFI Environment Projects and other European Projects such as ENHSIN, and BioCASE. A programme of meetings between Elixir staff and members of these is being undertaken in order to work out the details of the interactions necessary to achieve these aims.

### 3.2.5 European Infrastructure for phenotyping and archiving of model mammalian genomes (INFRAFRONTIER)




Mouse models are an essential tool in the functional analysis of the mammalian genome and the study of human diseases. Research groups all over Europe and large international collaborative efforts will produce an ever growing number of mouse disease models over the next years. These mice have to be systematically characterised on the functional and molecular level, and they have to be made available for the entire European research community. INFRAFRONTIER will establish a distributed pan-European infrastructure to meet these increasing demands for systemic phenotyping and archiving.

The partners of INFRAFRONTIER will use the preparatory phase (funded by the European Commission with 4.5 Mio € for 36 months) to tackle central issues of the emerging infrastructure such as overall strategy and governance, legal matters, and sustainable funding. Technical questions such as draft engineering specifications for the emerging facilities and the bioinformatics required to manage the data will be addressed. Other important issues will be the transfer of know-how between existing and new facilities, and the involvement of additional partners, particularly from the new member states of the EU.

The consortium of INFRAFRONTIER currently consists of fifteen scientific partners, representing established and new European phenotyping and archiving facilities, and twelve ministries and funding agencies of seven different European countries. In addition, three countries (Czech Republic, Austria, Canada) participate as 'observers' in the different work packages and may become full members during the course of the preparatory phase.
The partners of INFRAFRONTIER met on June the 2nd and 3rd in Freising/Germany for the kick-off meeting. The work program was discussed, the expert groups of the different work packages had their constitutive meetings, and the governance structure for the preparatory phase was established.

Already during this early stage, INFRAFRONTIER closely interacts with other ESFRI BMS RIs. Experts involved in BBMRI, ELIXIR and EATRIS participated at the kick-off meeting. The Advisory Board of INFRAFRONTIER will contain representatives of the other BMS RIs. INFRAFRONTIER will cooperate with EATRIS on the design of animal facilities and on legal issues of animal welfare, and with ELIXIR and BBMRI in the area of bioinformatics. Furthermore, close cooperation on the legal and financial issues common to all BMS infrastructures has been agreed upon in a common meeting (Brussels, June 11th 2008).

### *1. Name and descriptive title*

## INFRAFRONTIER – European Infrastructure for phenotyping and archiving of model mammalian genomes

### *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*

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*

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 wellorganised 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.

## *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 Members***

| Scientific Partners | Funding Organisations (ministries, research councils) | Associated Partners |
|---|---|---|
| - Helmholtz Zentrum München - German Research Centre for Environmental Health GmbH<br>- MRC Mammalian Genetics Unit<br>- Consiglio Nazionale delle Ricerche Instituto di Biologia Cellulare<br>- Centre Europèen de Recherche en Biologie et en Mèdecine GIE – ICS<br>- Genome Research Limited / Sanger Institute | - MRC<br>- CNR<br>- CERBM-GIE<br>- Fundação Calouste Gulbenkian<br>- CNRS<br>- Hellenic Republic Ministry of Development<br>- Helmholtz Association<br>- German Ministry for Research and Education | - |
| - Biomedical Sciences Research Centre Alexander Fleming<br>- Karolinska Institute<br>- Fundação Calouste Gulbenkian Instituto Gulbenkian de Ciência<br>- CNRS-CDTA<br>- Universitat Autonoma de Barcelona<br>- Consejo Superior de Investigaciones Cientificas (CNB-CSIC)<br>- University of Oulu<br>- European Molecular Biology Laboratory<br>- Helmholtz Centre for Infection Research GmbH<br>- University of Copenhagen – Transgenic Core Facility | - Swedish Research Council<br>- Generalitat de Catalunya, Departament de Salut<br>- Parque Cientifico de Madrid<br>- Communidad de Madrid | |

***8. Budgetary information***

| Preparatory cost (total in Mio €) | Construction cost (total in Mio €) | Operation cost (total) | Re- and decommissioning cost (total in Mio €) |
|---|---|---|---|
| 4,8 Mio € | 270 Mio € Phenomefrontier – 150 Mio € Archivefrontier - 120 Mio €<br><br>Construction of new facilities and major upgrades of the existing facilities | 36 Mio € per year Phenomefrontier – 24 Mio € per year Archivefrontier - 12 Mio € per year<br><br>Assigning new phenotypes to new mouse models from different pipelines. Archiving new mouse models including | Not applicable |

| | | | |
|---|---|---|---|
| | | attached data sets within an upgraded database. | |

## *9. Timetable until operation*

| Preparatory phase | Construction phase | Operation | Re- and Decom-missioning |
|---|---|---|---|
| 2008 – 2010 | 2010 - 2020 | 2010 – 2020 | |

## *10. Contact*

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http://www.infrafrontier.eu

## *11. Progress in the preparatory phase*

**Overall strategy and general description:**
The Infrafrontier preparatory phase is a project of three years duration and will commence in March 2008. The work plan is broken down into eight work packages. Of central importance are Infrafrontier work package 2 **(Strategy and Governance),** work package 3 **(Legal work)** and work package 4 **(Financial work and funding).** WP2 will define the Infrafrontier mission, its vision, the governance structure of the planned infrastructure in operation and the services of the new infrastructure. The overall strategy will be defined by an iterative process involving WP2, WP3 and WP4 and will be summarised in a strategic plan for the construction phase. WP3 will determine the most suitable legal status of the planned infrastructure. Furthermore, drafting, negotiating and signing an agreement e.g. a Memorandum of Understanding (MoU) or a treaty between all partners involved, may contribute to long term stability of the consortium. WP4 will work out a sustainable funding concept for the new infrastructure and provide a business plan for the construction phase. All partners will be involved in WP2, WP3 and WP4. Related to their central importance these three work packages will provide the **key deliverables of Infrafrontier** which are:

1) The identification of the most suitable **legal status**
2) A **business plan** based on a sustainable funding concept
3) A **legal agreement** between all partners
4) A **strategic plan** for the construction phase.

These support activities will be complemented by two technical work packages. **WP5 (Draft engineering specifications)** will support the construction of new animal facilities. **WP7 (Bioinformatics)** will assess the IT systems of the existing mouse clinics and archiving centres and provide recommendations on the best mouse management and LIMS systems for the new partners. Furthermore, work will be undertaken to facilitate and ease the exchange of data

among the Infrafrontier partners. In addition, dissemination activities are planned. **WP6 (Training)** will ensure the transfer of know how between partners aiming at the establishment of common standards among all scientific partners of the new infrastructure. **WP8 (Networking)** will ensure the alignment of the planned services of the new infrastructure with the needs of the European mouse functional genomics and biomedical research community. Potential new Infrafrontier partners particularly from new EU member states will be identified and the Infrafrontier activities will be embedded in global efforts related to archiving and distribution and mouse phenome database integration. **Work package 1 (Management) concerns the project management** of Infrafrontier.

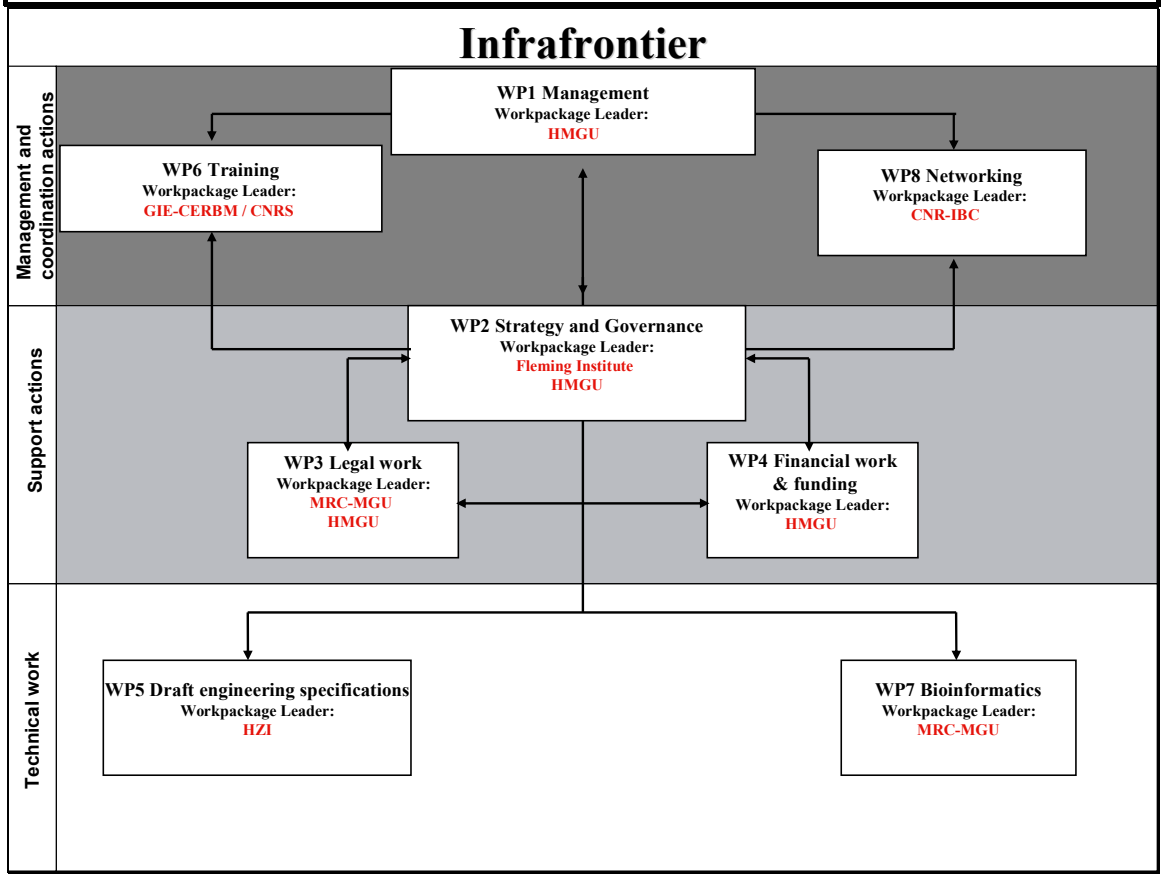
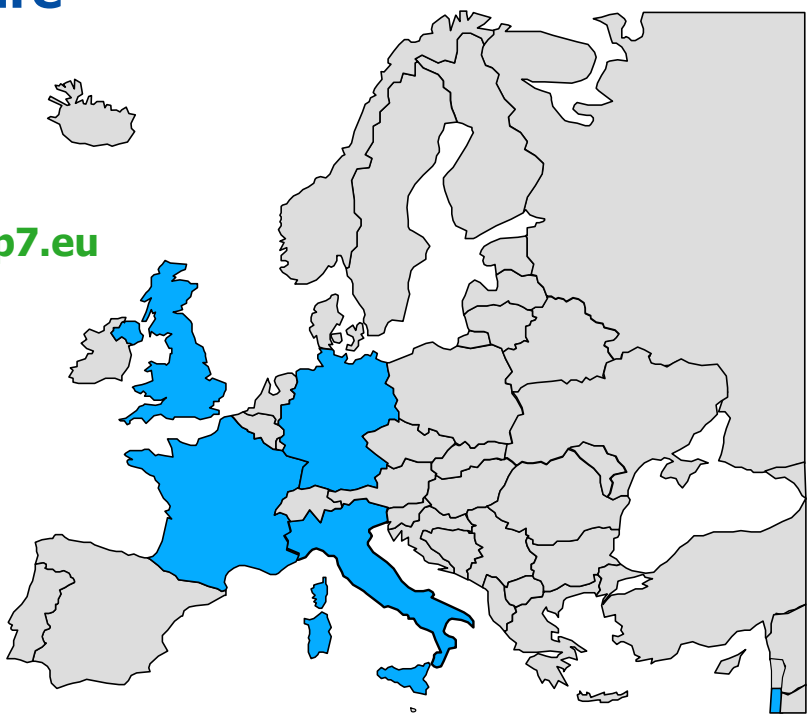


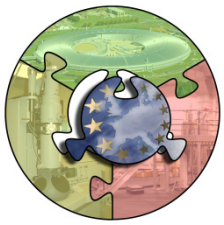

Figure 1: **Pert Chart** illustrating the interdependencies of the Infrafrontier work packages

### 3.2.6 Integrated Structural Biology Infrastructure (INSTRUCT)

# INSTRUCT: Integrated Structural Biology Infrastructure

**EC: 4.5 M€**
**24 months**
**13 partners**
**www.instruct-fp7.eu**





Structural biology in the next two decades aims to integrate structural knowledge at different resolution levels into specific cellular contexts, with a temporal component, to underpin biomedical issues. This challenge requires the seamless integration of techniques providing information in different resolution ranges. INSTRUCT will link the information obtained by the major structural biology methods with state-of-the-art cell biology techniques to provide a dynamic picture of key cellular processes at all scales. Major technology advances, from high throughput methods in protein production, through NMR and X-ray crystallography to electron microscopy mean that major investment in infrastructure is required to maintain European competitiveness. The preparatory phase of INSTRUCT started the 1st of April 2008 and the consortium met in Paris the 5th of May for the Kick off meeting. At the meeting the working groups consolidated their membership and planned work for the next 2 years. The membership of the working groups includes a core from within the consortium with the addition of external advisers when required. A complete list of the membership and schedule of the working groups is available from our web site (http://www.instruct-fp7.eu ). Other BMS RIs were represented at the Kick off meeting with presentations from ELIXIR and ECRIN.

The running of Instruct is the responsibility of the Management Committee which met for the first time the 23rd of March 2008. The committee is formed by a representative of each of the core members. The management committee has proposed the membership of the External Advisory Board (EAB) which will meet once per year at the consortium annual meetings. The EAB will influence national funding bodies to help them to commit to the program. The annual meetings will take place in May 2009 and 2010. The membership of the pan-European Evaluation Group was proposed. This group will take decisions regarding ac-

cess to the infrastructure by strict scientific evaluation.
The next stakeholders meeting will take place in Munich the 16th of October. It is expected that 200 participants representing the whole consortium will discuss the outcome from the working groups as well as the deliverables from the different work-packages.

### *1. Name and descriptive title*

**INSTRUCT: Integrated Structural Biology Infrastructure.**

### *2. Short description of new RI or major upgrade and main characteristics*

The new infrastructure is expected to consist of six or seven distributed Core Centres for Integrated Structural Biology, each with a broad complement of core technologies and linked biological foci to drive the development of infrastructure expertise. All Centres will maintain and further develop a set of core technologies such as protein production, NMR, crystallography, and different forms of microscopy. Each Centre will shape their infrastructure development plan from the scientific need to improve the production and analysis of functional complexes. Development of infrastructure in each Core centre will include the identification and design of new-build infrastructure capabilities, upgrading of existing facilities to incorporate the newest technological capabilities and the maintenance of existing technologies in such a way to provide access for the user community through the development and implementation phase of the project. The network of Centres will be organized in order to obtain multi-scale structural data and translate these data into functional knowledge. In doing this, the specific aims of the project will be:

1. To fully define fully the appropriate composition of Core and Associate Centres to provide an optimum European Infrastructure. Criteria:
   i) Scientific excellence, ii) Scientific coverage, iii) Strong record in technology & methods development, iv) Commitment to collaborative infrastructure, v) Biomedical engagement, vi) National commitment
2. To establish the correct balance of infrastructure provision required to permit existing and developing technologies to mesh effectively between the different levels of resolution in structural biology, from the molecular to the cellular and ultimately the whole organism scale, thus providing a dynamic picture of key biological processes. Criteria:
   i) Likely interdisciplinary impact of technologies, ii) European leadership in each area
3. To establish a plan to enter rapidly the operations phase of INSTRUCT whilst running the construction phase activity alongside this. Criteria:
   i) Key core technologies provided at the end of the Preparatory Phase, ii) Integrative technologies developed in parallel.

INSTRUCT aims to establish a balance of National and Pan-European activity that will ensure that the major centres can be supported by National funding mechanisms whilst building a viable business plan that allows Pan-European access.

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

**The scientific challenge:**
The major challenge for structural biology in the next two decades will be the integration of structural knowledge at different resolution levels into specific cellular contexts. This will underpin biomedical sciences. This challenge requires the combination of techniques providing information in different resolution ranges - appropriate to each of the required scales - and bridging the gaps between them. Furthermore, besides this static picture of a cell, there is a temporal component that is crucial and understanding cell biology requires understanding the dynamics of the different cellular processes. Going beyond the single protein approaches to identify, characterize and analyze the individual structural assemblies and subassemblies of a cell, it is now important to integrate the information obtained by the major techniques (NMR, X-ray and electron crystallography, electron and light microscopy) and develop the necessary mathe-

matical methodology to combine the resulting information. In addition, integration with state-of-the art cell biology techniques (of which light microscopy of living cells is already an important part) is another essential aspect, providing a dynamic picture of many of the key processes (intra-cellular trafficking, for instance) at all scales.

**Establishing infrastructure to meet the challenge:**
One impact of the major technology advances, from parallel methods for protein production, though NMR and X-ray crystallography to electron microscopy and tomography is that substantial investment in infrastructure is now required to maintain European competitiveness in this core aspect of biology. The development of the INSTRUCT infrastructure is driven by biological questions linked to human health (cancer, infectious diseases, host-pathogen interactions, etc.) and/or environment problems (adaptation of life to extreme conditions: temperature, heavy metals, radiation, toxic molecules. These infrastructures will provide world-class facilities and maintain Europe's competitiveness in structural biology. The requirements for highest precision instrumentation will challenge European industry to improve their capabilities and the use of the facilities for industrial research will strengthen Europe's industrial competitiveness in particular in bio-pharma companies (INSTRUCT will engage directly with these companies) and areas such as electron optics. Key technical bottlenecks will be addressed jointly with appropriate European SMEs. The project will include an interdisciplinary training programme in biology, chemistry and physics relevant to the expertise needed in structural biology.
Each Core Centre will develop its own scientific program and continue to develop technological and methodological cutting edge expertises in various approaches. The centres will be complementary to one another. In addition to the Cores, technology will be made available from Associate Centres, where smaller, more focused technologies will be developed for access. Both Cores and Associates will deliver a significant fraction of their activity via open-access for the user community. Access will be facilitated by a network of National Coordinators who represent the interests of national stakeholders, both to the local funding bodies and, in INSTRUCT, to help establish strategic priorities.

## *4. The Concept case*

Structural biology has an illustrious history in Europe. We are now at a turning point in the impact of structural studies on biology, as sample production technologies mature and key core techniques become increasingly powerful, but escalate in cost. The challenge is to maintain the momentum built up, especially by the coordinating actions of EC funding in FP5 and 6, to establish the Core Centres, Associated Centres and National Coordinators who can provide and effectively use a robust infrastructure to take the integration of methods to the next level, keeping Europe competitive as structural biology evolves into integrative structural cell biology. This proposal represents the next step: to make concrete preparations to implement the infrastructure.
A major objective of this phase will be to establish the optimal *modus operandi* for INSTRUCT. The partnership brings together a very strong scientific collective body with European and global eminence in the area of structural biology to orchestrate the operation of a large integrated initiative at all levels of science, technology and governance. The centres will be networked to a wider community to capture multi-scale data and translate these into functional knowledge.

## *5. Further information, including strategic importance to ERA*

**Scientific strength of Europe in structural biology**
The research community in structural biology within the ERA is extensive and well-established. The community spans seamlessly from academic research through to the numerous Europe-based biotech and pharma companies and drives a huge diversity of commercial development of methodologies and instrumentation. INSTRUCT draws on the vibrancy of the interface between structure biology research and commercial development by the inclusion of a European company as a Partner and by the involvement of a cohort of companies (the majority SMEs) in

the proposed feasibility studies to inform the infrastructure development plan. European laboratories have consistently played a pioneering role throughout the development of structural biology (as testified by the number of European Nobel prize winners in this field). The research community has a unique history of inter-laboratory pooling of developments to drive forward cutting edge research (for example the efficient pooling of crystallographic software via CCP4) most recently supported and promoted at a pan-European level by EC funding (as discussed in the following section) and in terms of large scale facilities exemplified in the development and use of intense X-ray and neutron sources. For such sources structural biology research has already necessitated levels of capital investment beyond the normal means of a single research institution and in many cases requires the international cooperation of several countries for the largest facilities. European structural biology has benefited from a very large effort based around synchrotron facilities (ESRF, DESY, PETRA, BESY, SLS, LUCIA, SOLEIL, DIAMOND, TRIESTE source and SCANDANAVIA source) and neutron sources (ILL, Jülich and ISIS). INSTRUCT will build on these foundations to tackle the diverse and evolving challenges of providing an infrastructure for the transition from molecular to cellular structural biology.

**Potential for INSTRUCT to add value**
INSTRUCT will provide a well-coordinated pan-European effort to provide the capacities and expertise needed to contribute to the continued development of existing technologies and the implementation of emerging technologies in structural biology. INSTRUCT will develop infrastructures to a greater level of integration than has so far been possible in European structural biology by tying in several existing national initiatives into the European framework.

INSTRUCT will integrate Core Centres combining excellence in all major areas of structural biology with Associate Centres providing further technical expertise and access to infrastructure. Flexibility in the composition of participants is inherent in the project structure: a key objective of the Preparatory Phase will be to evaluate groups for their ability to provide access to technology and specific expertise at each level and provide a mechanism to include new participants at all levels of Core centre, Associate centre or Access holder.

INSTRUCT will also benefit from forming links with other BMS projects. European structural biology has maintained strong links with EMBL-EBI over many years, most recently through the SPINE, eHTPX and PIMS projects and will continue to build on this excellent relationship to develop resource and data handling in parallel to the hardware technologies being developed by INSTRUCT.

## *6. Identification of other socio-economic impacts*

The structural biology community has a very strong track record for using EC input as a catalyst for national investment and for genuine scientific coordination. This was demonstrated by the effects of the FP5 IP SPINE (Structural Proteomics in Europe), which galvanised a number of laboratories across Europe, at a time when Europe was falling dangerously behind in terms of infrastructure and technology development for HTP structural proteomics. The remarkable speed of uptake of technologies demonstrated as effective in the SPINE context (for instance small-volume crystallisation methodologies) allowed Europe to catch up and remain competitive. Since SPINE there have been a significant number of other projects, covering most areas of structural biology, which have maintained a strong culture of development and exchange, which allows Europe, in many cases, to punch above its weight, in terms of scientific output. In addition EC funding via I3 grants has provided a very effective mechanism for facilitating access to infrastructure.

INSTRUCT will continue this mission in providing cutting edge technologies, training young scientists and identifying new goals for structural biology development in the future. It will encourage European scientists to find solutions to previously difficult cross-border infrastructure sharing arrangements and to benefit from the exchange of knowledge, co-development opportunities and the possibility of cost recovery for the technologies.

| ***7. Participating Members*** | | |
|---|---|---|
| Scientific Partner<br>P1.University of Oxford, UK<br>P2. CERBM, Strasbourg, France<br>P3. EMBL (Grenoble, Hamburg, Heidelberg sites)<br>P4. CIRMMP, Florence, Italy<br>P5. Weizmann Institute, Israel<br>P10. Max-Planck-Society (Munich and Frankfurt sites), Germany<br>P12. Bruker Biospin GmbH, Germany | Funding Organisations (ministries, research councils)<br>P6. Medical Research Council, UK<br>P7. CNRS, France<br>P9. MOST, Israel<br>P11. BMBF, Germany<br>P13. CNR, Italy | Associated Partners<br><br>Yet to be defined |

| ***8. Budgetary information*** | | | |
|---|---|---|---|
| Preparatory cost (total in Mio €)<br>4.5 Mio € | Construction cost (total in Mio €)<br>300 Mio € | Operation cost (total)<br><br>25 Mio €/year | Re- and decommissioning cost (total in Mio €)<br>50 Mio € |

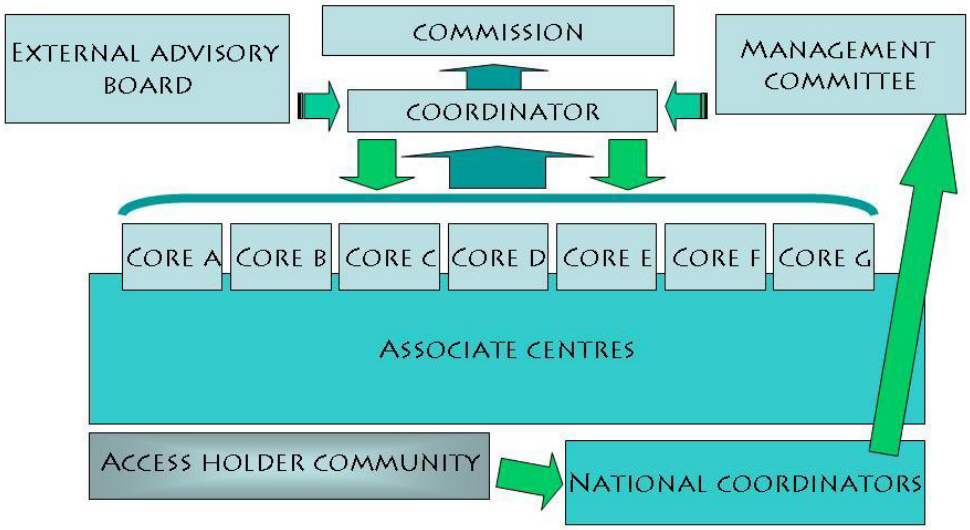
| ***9. Timetable until operation*** | | | |
|---|---|---|---|
| | | | |
| Preparatory phase<br><br>2008-2010 | Construction phase<br><br>2010-2017 | Operation<br><br>2012-2017 | Re- and Decommissioning<br>2012-2017 |

| ***10. Contact*** |
|---|
| Professor David I Stuart, Division of Structural Biology, University of Oxford, UK<br>http://www.strubi.ox.ac.uk |

| ***11. Progress in the preparatory phase*** |
|---|
| The workplan is divided into 14 workpackages. WP1-6 and WP13 are administrative in nature and WP7-12 address the scientific and technical planning required to optimise the nature and quality of the infrastructure provision. WP14 will provide feasibility studies to identify technological opportunities and feed into the construction and implementation phases. The projected start date of the project is March 2008. |

| WP No | Short description and specific objectives of the task |
|---|---|
| 1 | **Management:** Define the management structure and decision process. Establish communication and reporting strategy |
| 2 | **Process Plan:** Recruit staff, establish External Advisory Board, organise kick-off meeting, launch the first series of working groups, define the Implementation phase workplan |
| 3 | **Legal status and governance:** Establish rights, duties and liabilities. Provide framework for external governance |
| 4 | **Financial planning:** Provide a business plan for the Construction and operations phase. |
| 5 | **Buildings and facilities:** Establish requirements for Core and Associate Centres. Draw up plans for construction |
| 6 | **Access rules to infrastructure:** Develop a cost and management model for evaluation of Access Holders and project based applications. Develop a process for safety management and Standard Operating Procedures. |
| 7 | **Coordination of data management:** Develop plans for standards, interfaces, analysis tools and mechanisms for sharing and pooling data |
| 8 | **Core infrastructure technologies – X-ray:** Establish a model for including synchrotrons |
| 9 | **Core infrastructure technologies – NMR:** Establish plans for infrastructure and perform feasibility studies |
| 10 | **Core infrastructure technologies – EM:** Establish plans for infrastructure and perform feasibility studies |
| 11 | **Core infrastructure technologies – sample production and emergent technologies**: Establish plans for infrastructure and emergent technologies and perform feasibility studies |
| 12 | **Interface technologies, systems biology and computational approaches:** Establish a mechanism for outreach to other areas including BMS infrastructures and biological chemistry. Interface with computational biology. |
| 13 | **Capacity building and training:** Develop a forward plan for expansion. Plan for incorporating new member states |
| 14 | **Feasibility studies for development technologies:** Perform seven feasibility studies jointly with European industry. |
| | |

The organization of participating centres and groups is shown in the PERT diagram below. The management structure will act as a model for the organization of the subsequent phases of INSTRUCT and will provide a smooth transition into the final operational structure. The structure embodies a transparent and inclusive decision process in order to reflect the needs and ideas of a wide cohort of participants.



### 3.2.7 Conclusion:

All BMS RI currently in the pp are making good progress and developing satisfactorily.
They are developing ways to strengthen their collaboration and searching for overlaps to integrate themselves in a strong cooperation.

There have been annual meetings of all six scientific coordinators (2007 Frankfurt; 2008 Brussels). A close exchange of best practice examples has been agreed. Each pp RI has identified the key Work Packages that should work closely together (e. g. WP on legal issues and governance). Between several RIs there are already bi- or trilateral cooperative links (e. g. joint strategic board of ECRIN, EATRIS, BBMRI).

BMS RIs jointly applied to the IMI call (FP7 Innovative Medicine Initiative).

BMS RWG will in future concentrate even more on its “incubator role” and organize more frequent coordinating meetings among the six scientific coordinators and with BMS members from 29 MS to ensure a better link to the funding bodies in each respective MS.

# 4 Evaluation OF NEW PROPOSALS

The RM update process was prepared by ESFRI in summer 2007 and Terms of Reference (ToR) for the work of RWGs on the update of the ESFRI RM were launched in September 2007. The deadline for submitting proposals was November 30th 2007, which left a very short time for the task of the BMS RWG. It would have welcomed much more time to study and evaluate the proposals.

The BMS RWG received 7 BMS proposals forwarded by Executive Board (EB) (RU01, 02, 04, 05, 16, 18, and 41). In addition the BMS RWG received one proposal jointly together with the ENV-RWG, for which the BMS RWG was in charge (RU 22) and 4 proposals, for which both BMS RWG and the ENV-RWG were in charge (RU 23, 25, 30 and 32). One of those four proposals (RU 30, ASSA) was originally sent solely to the ENV RWG by the EB, but the Norwegian ESFRI delegation asked the EB to also provide it to the BMS RWG for evaluation. BMS RWG agreed to give a statement and recommendation on this proposal. In contrast the BMS RWG decided at its 10th Meeting in December 2007 that the BMS RWG members have no expertise to evaluate RU 23, 25 and 32. ENV-RWG was informed accordingly.

Another 3 proposals (RU 17, 31 and 33) were sent to all RWGs, but with eIWG as leading RWG. The BMS RWG nominated three Experts out of its group to support the eIWG in evaluating these proposals, focussing on e-Infrastructure.

The BMS RWG Secretariat created a password protected working platform and provided it to the BMS RWG members in November 2007. All members received restricted access to this platform, which contains all documents the group created (all agendas and minutes of the meetings, the new proposals, the assessment forms, the draft of the BMS report etc.) and which was supported by the BMS RWG Secretariat, to guarantee the transparency of the process.

The composition of BMS RWG has been decided by ESFRI Forum. The membership of BMS RWG consists of both science policy and scientific experts (Appendix A). Any potential conflict of interests was dealt with according to the ToR of RWG's, last updated 9 March 2007.

## 4.1 Methodology

In order to guarantee a high quality level for the evaluation process, the BMS RWG established four different Expert Groups covering the different scientific fields of the proposals. Each Expert Group consisted of five members; two internal experts (from BMS RWG) and three external experts. The three external Members of each Expert Group were selected from the approved list of experts (nominated to ESFRI by the Member States in 2004) considering their expertise, the balance of countries and gender and excluding any possible conflict of interest. The membership in the Expert Groups included some of Europe's and the world's leading biologists and medical scientists. The Expert Groups were chaired by a BMS RWG member, who reported directly to the BMS RWG and the BMS Chair.

The following four Expert Groups were set up:

Expert Group 1: Systems-, Chemical- & Synthetic Biology (chaired by Professor Dimitrios Thanos, GR)

Expert Group 2: Imaging (chaired by Professor Jørgen Frøkiær, DK)

Expert Group 3: High Security Labs, Infectious Diseases (chaired by Professor Virgilio do Rosario, PT)

Expert Group 4: Biological Sciences (chaired by Dr. Edvard Beem, NL)

The Expert Groups worked from November 2007 to May 2008. On January 14th, there was a one-day meeting in Berlin, where all four different groups came together to discuss their results and prepared final

recommendations to the BMS RWG. In its work, the Expert Group followed the set "Terms of reference of expert groups and chairpersons".

The Expert Groups have reviewed the needs of the biological and medical scientific communities for pan-European infrastructures and analysed the specific proposals received through ESFRI. The Expert Groups reviewed the proposals for new research infrastructures or major upgrades of pre-existing research infrastructures and prepared recommendations for the BMS RWG.

### 4.1.1 Procedural guidelines for the Expert Groups

Chair of an Expert Group:
Expert Groups were chaired by members of the RWG. The Chair of an Expert Group was not allowed to be involved in a specific RI to be evaluated by this Expert Group.

He/she was responsible for the timetable and good organisation of the evaluation process.
The BMS secretariat supported the Chairs if required.

Membership:
Members of Expert Groups were not allowed to be involved in a specific RI proposal either as coordinator or as possible partner. Any conflict of interest was reported right at the beginning of the evaluation procedure to the Chair of the Expert Group. Members of the Expert Groups were selected on the basis of their expertise, including science policy development, and of their international reputation.

The Expert Groups consisted of no more members than it was necessary to provide an overview of the area under consideration; Expert Groups ideally had about five members, two from the BMS RWG and three external experts.

The BMS RWG Chair could announce another expert in case one of the approved experts was not available, after consultation with the Chair of the respective Expert Group.

Method of working:
Members of the Expert groups performed evaluations on a personal basis and did not represent their national nor private interests. They were expected to be independent, impartial and objective.

A meeting of the Expert Groups to discuss their findings was held in a closed-session; all information exchanged within and prepared by the Expert Group was meant for internal use only, unless explicitly stated.

Basic requirements for consideration:
Under supervision of the BMS RWG, the Expert Groups assessed whether or not a potential (major upgrade / new) pan-European Research Infrastructure should be included in the RM.

To fulfil their tasks, and before analysing specific initiatives (which should have received the previous support of an ESFRI member), 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.

Each identified Research Infrastructure was reviewed according to the stagegate process for evaluation of new proposals laid down by the ESFRI Forum:

1. The Scientific Case (stagegate process, step 4): The proposed new RI should correspond to future needs of the scientific communities in Europe, demonstrate impacts on scientific developments, support new ways of doing science in Europe and participate to the enhancement of the European Research Area.

Additional information, supported by the appropriate scientific community at European level, should demonstrate its pan-European value, setting the scene for the infrastructure in an European and an international context, as well as its relevance and quality.

2. The Concept case (stagegate process step 5): The proposed new RI should be technologically and financially feasible and meet the necessary degree of maturity which is defined as (a) the existence of a technical concept for the realisation of the RI and of feasibility studies, including identification of technical challenges and risks, (b) the exis-

tence of a projection about construction, operating and decommissioning costs, including a clear timetable.

In addition, the ESFRI analysis would require relevant information on (c) the recent or near future peer review of the RI, and by which panel; (d) the potential for risks- and costs-sharing and for developing effective joint actions in Europe; (e) the mechanisms for other partners to join later on and (f) the mechanisms to ensure the human resources and the capability to use the RI in the most open and effective way.

#### 4.1.2 Modus operandi

The Chair of the BMS RWG provided information covering the evaluation procedure, the experts' responsibilities, the issues involved in the particular area/objective, and the assessment forms.

The first part of the evaluation (end Nov 2007 – mid Dec 2007) was carried out on the premises of the experts concerned ("remotely").

At this first step the experts were acting individually. The experts recorded their individual opinions in an Individual Assessment Report (IAR); concise but explicit justifications were given for each score and also comments against the evaluation criteria.

The experts also identified questions they identified as not sufficiently described in the proposal template, as well as giving recommendations for improvements if useful. They sent these to the Chair of the Expert Group, who then clarified these issues with the coordinator of the proposal and provided a suitable feedback to the members of the Expert Group.

Based on this feedback information the experts provided suitable comments to be discussed at the expert group meeting (see below). All experts completed their IAR and sent it to the respective Chair of the Expert Group.

The second step included a meeting in Berlin, at which the experts presented their common views, discussed and prepared comments for the particular RIs relating to the Scientific Landscape. Finally they produced one final assessment form for each proposal.

The discussion was moderated by the Chair of the Expert Group. He/she sought to arrive at a consensus between the individual views of experts without any prejudice for or against particular proposals or the organisations involved.

The Chair was responsible for drafting the final evaluation report, which also contained the scores and comments from the final assessment form. The Expert Groups also came to a common view with respect to the Scientific Landscape. If during the discussion it was found to be impossible to bring all the experts to a common point of view on a particular aspect of the proposal, the Chair noted this in the report to the BMS RWG.

The final evaluation report was provided to the BMS RWG Chair for discussion in the BMS RWG`s January meeting.

#### 4.1.3 Evaluation Criteria

The proposals were evaluated against predetermined evaluation criteria.

Each criterion was scored out of 5. Half marks could be given.
The scores indicated the following with respect to the criterion under examination:
0 Insufficient. The proposal fails to address the criterion under examination or cannot be judged due to missing or incomplete information
1 Poor. The criterion is addressed in a cursory and unsatisfactory manner.
2 Fair. There are serious inherent weaknesses in relation to the criterion in question.
3 Good. While the proposal broadly addresses the criterion, there are significant weaknesses that would need correcting.
4 Very good. The proposal addresses the criterion well, although certain improvements are possible.
5 Excellent. The proposal successfully addresses all relevant aspects of the criterion in question. Any shortcomings are minor.
No weightings were applied.
The following criteria were checked to assess the maturity of the 9 incoming proposals:

*Scientific Case:*

- Does the proposed RI offer an important service responding to the future needs of users?
- In how far does the proposed RI address the needs of European / global users within the given field?
- Is / Are the target group(s) of users identified?
- Will the proposed RI contribute to the excellence and coordination of high-quality work in Europe
- Is the pan-European / global value clearly demonstrated?
- Please clarify how the new RI will fit into the existing and future landscape of Research and of existing RI's.
- Does the proposed RI offer an improvement beyond the state of the art?
- In how far does the proposed RI contribute to the problems to be solved?
- In how far does it contribute to harmonisation and standardisation within Europe?

*Concept Case / Maturity:*

- Is the necessary scientific and technological expertise identified?
- Is the concept technologically feasible?
- Is the requirement for e-infrastructure sufficiently described?
- Can it be integrated with the existing EU e-infrastructure?
- Are the important key players identified and integrated in the proposed RI?
- Are costs estimates feasible?

*Additional questions*

- In how far does the proposed RI contribute to innovative research / innovation / demonstration, training and other relevant activities?
- Has the proposed service and / or access for users to the RI been made clear?
- Would you have recommendations for the proposed RI?

#### 4.1.4 Further assessment Criteria

In addition the following list of elements as it was agreed on the ESFRI meeting (6th December 2007) was used during the evaluation of the proposals.

- Evidence that the management of the infrastructure will ensure open access to all interested researchers, based on quality of the users proposals.
- Evidence that the infrastructure is either new or proposing a major upgrade, and that this is fully justified by the quality and potential increased service to the scientific community.
- That the proposal is not only seeking a "EU label" to become more visible based on this aspect in place of its quality and pan-European value.
- Interconnection or possible links with several proposals (some already on the RM) and across disciplines, leading to the construction of some sort of complex "infrastructural systems" (the RWG's should try to understand how they fit in the scientific landscapes).
- Links with national RMs or other vision & strategy documents
- If necessary, consider the proposal in the context of the overall landscape in order for the RWG to define the priorities between the various proposals

### 4.2 Evaluation Results

During the process of evaluation all 9 proposals were available for the BMS RWG members from the password-protected BMS working platform. The recommendations prepared by the Expert Groups were taking into account during the 11th BMS RWG meeting in Jerusalem, 24th-25th of January 2008, where all proposals were discussed and assessed.

BMS RWG has identified four proposals as promising infrastructures, which passed step 6 of the stage gate process and met the ESFRI criteria for inclusion on the Update of the ESFRI RM. Further the BMS RWG decided that one proposal passed step 5 of the stage gate process, which means that it is considered as an Emerging proposal. And finally BMS RWG decided that three proposals did not pass step 5 of the stage gate process

and will not be considered for the inclusion in the ESFRI RM.

### 4.2.1 Mature Proposals

The BMS RWG emphasises that besides these four proposals, which are identified for a recommendation for inclusion in the update of the ESFRI RM, there are further important scientific fields, in which infrastructure is not yet sufficiently developed, but urgently needed. These fields, e.g. Systems Biology, will play a major role in the future. BMS RWG will promote its development for the next update of the ESFRI RM (incubator role). The infrastructures proposed have been influenced by the need to demonstrate maturity under the ESFRI criteria and the priorities of MS. The BMS RWG put a high value on the open access approach of the proposed RI for users from the scientific community as well as for possible future partners and participants at a later stage from all MS.

**RU04 EU-Openscreen – European Infrastructure of OpenScreening Platforms for Chemical Biology**
Submitted by the ESFRI delegation of Germany)

**Short description**
The proposal offers European researchers involved in Chemical Biology access to screening facilities, small molecule libraries, a central database, and the associated scientific and technological expertise. Chemical libraries are very important to provide tools to decipher biologically important biochemical pathways thus complementing classical genetics and molecular biology approaches. They are also important to identify small molecules as targets for drug development. Current libraries serve the need of big pharma industry but are largely inaccessible to academic users and SMEs because of the costs. This RI will significantly increase the size of compound libraries available in Europe and facilitate the coordination of existing libraries in an integrated infrastructure. It will also create a wide panel of diverse screening assays. It is beyond dispute that the field of Chemical Biology is very important for the life sciences community in Europe.

**Synthesis opinion**
The proposed RI contribute to the excellence and coordination of high-quality work in Europe by enabling screens to be done that otherwise could not be done, or could be done only by collaboration with a large industrial partner. Creating a wide panel of diverse screening assays and significantly increasing the size of compound libraries available in Europe means the proposed RI offers an improvement beyond the state of the art of what is possible within this field in Europe and keeps Europe competitive.

**Justification in detail**
The proposed RI will facilitate the coordination of existing libraries in an integrated infrastructure. The identification of chemical inhibitors will solve problems relevant for function especially in problems not accessible through genetics. Moreover it will bridge the gap between academic research and pharmaceutical drug development pipeline.

**RU16 + RU 41 Euro BioImaging - European Biomedical Imaging Infrastructure – from molecule to patient**
Submitted by the ESFRI delegations of Austria and Switzerland

**Short description:**
Early in the evaluation phase of the area of “Imaging” it was clear, to the BMS RWG as well as to the respective Expert Group, that two received proposals should be combined, because in large part they complemented each other: One proposal dealt mainly with clinical aspects of imaging technologies entitled “European Infrastructure for Research in Biomedical Imaging” – EIRBI (RU 41) and another proposal dealt with imaging at the basic research level entitled “Advanced light Microscopy Infrastructures for Europe” – AMIE (RU 16). The BMS RWG had already stressed in its December 2007 meeting that these two proposals had great importance for the European Life Sciences and came to the conclusion that they were very complementary. This was fully supported by the Expert Group. The two coordinators agreed to combine and integrate these two proposals into one.

The combined proposal brings together key research areas in the imaging field stretching from basic biological imaging with advanced

light microscopy to the clinical level with medical imaging. Data storage and handling, and marker development, are major parts of the infrastructure. The aim is to be able to image non-invasively, in real time and in 4 dimensions, at every level from molecule to man through creating a coordinated and harmonised plan for infrastructure deployment in Europe.

**Synthesis opinion:**
There is an unmet need for non-invasive high resolution imaging techniques without radiation burden which can accurately predict, diagnose and monitor therapeutics/treatment procedures in patients at the organ, tissue, cellular and subcellular levels. The joint proposal will help establish imaging facilities all over Europe for this need. The proposed RI will contribute to the excellence and coordination of high-quality research in Europe and result in an improvement beyond the state of the art.

**Justification in detail:**
The aims of the EIRBI proposal are to sustain multidisciplinary approaches by bringing together chemists, biologists, physicists, imaging technologists and clinicians and hence to tackle the most challenging problems in the fields of oncology, cardiovascular and neuronal diseases.

This is a clear and well described RI that aims towards the creation of a pan-European RI in the imaging field. It will draw on valuable expertise available especially in the new MS and make very expensive technology accessible across the whole of Europe. The proposed RI has very ambitious goals.

**RU01 European high security BSL4 laboratories building and networking**
Submitted by the ESFRI delegation of France

**Short description:**
The proposal is about harmonising activities in European countries which address re-emerging and highly infectious diseases. The aspirations include increased research, better diagnosis and better training of investigators to address issues surrounding these agents. The rising threat of bio-terrorism is part of the motivation for establishing this RI. The proposal envisages building additional BSL4 areas on existing sites, as well as upgrading already existing RI´s, taking all players in this field within Europe into account.

**Synthesis opinion:**
Upgrading and creating of new BSL4 laboratories to improve the European situation in this field is of great importance. The need to have more BSL4 lab space in Europe is based on the general threat of emerging infections. The proposed RI will contribute to the excellence and coordination of high-quality research in Europe and result in an improvement beyond current capacity.

**Justification in detail:**
The proposed RI has very ambitious goals. It will impact the preparedness of Europe for emerging diseases in a very positive way. It offers an important service for the future needs of users. European target groups of users have been identified. There will also be collateral benefit of improving our understanding of infectious agents. An integral part of the proposal is the harmonisation of hardware and procedures. Although some level of deeper technological descriptions would have been welcomed the concept of the proposal has the potential to develop RI with high-level impact.

**RU22 EMBRC; European Marine Biological Resource Centre**
Submitted by the ESFRI delegation of Italy

**Short description**
The proposed infrastructure demonstrates the modern kind of distributed infrastructures, consisting of the major European Marine Biology Laboratories with a European transnational access role. It covers all fields from basic biology and marine biology to ecology, obtaining central DNA resources and cell lines from marine model organisms with various sample collection and ‘omics’ capability platforms. The results from the work on marine organisms will contribute to understanding of the food chain, as well as to biomedicine, biotechnology and environmental science. There is a pressing scientific need for the omics studies of marine organisms. The proposal presents a distributed RI with a clear pan-European value which could be funded in a straightforward way.

**Synthesis opinion**
The proposed RI offers an improvement beyond current capability in the understanding and exploitation of marine organisms, by studying model organisms. This will give benefits similar to those RIs dealing with mammalian species. There is certainly an added value in studying diverse marine organisms where the biological process and systems biology are more diverse and could be beneficial to man. Omics approaches in unicellular systems are likely to yield understanding of processes and systems of considerable exploitable value, and profound insights into the development of more complex multicellular systems.

**Justification in detail**
The implementation of this RI is an excellent opportunity to serve the needs of the entire European marine biology field and overcome fragmentation. The RI will thereby contribute to innovative research in the two emerging fields, (1) a merge of comparative and functional genomics with marine ecology and (2) a new molecular approach to marine biology. The results generated through working on lower organisms will have a great value for man. Moreover the proposed RI contribute to the excellence and coordination of high-quality work in Europe because it builds on established synergies between major marine biology centres with long standing history. Moreover there are two major trends (1) Marine Biology goes molecular and (2) Marine Ecology goes 'omics', which this RI serves perfectly.

### 4.2.2 Emerging Proposals

The proposal presented as 'emerging' provides a sign-post to the additional research infrastructures that is required for biological and medical science at a European level.

The BMS RWG considers that this proposal, which at present lacks the necessary maturity, should be examined by an Expert Group in the context of preparing the next update of the RM. The proposal identified as emerging is:

**RU02 European Research Infrastructure for Systems Biology (EISBI)**
Submitted by the ESFRI delegations of UK and Ireland

**Short description**
This distributed infrastructure will consist of Institutes established by national initiatives but committed to operate as an integrated multidisciplinary infrastructure for the European scientific community. The EISBI will consist of distributed Institutes, newly established or expanding at the national level, which are selected for participation in EISBI after evaluation by a high-level committee of experts. Each Institute will bring together a multidisciplinary group of excellent internationally recognized researchers ranging from biologists, medical doctors, mathematicians and engineers, to computer scientists and physicists, in an interactive, collaborative and welcoming environment, with a philosophy of interdisciplinary working. Each Institute selects its own research projects and focus; it will bring together significant experimental and mathematical analysis capabilities and relevant infrastructures, to work together with its own staff and with visiting researchers and students and thus provide a niche for scientists with diverse backgrounds and expertise under one roof. Each Institute will be focusing on a comprehensive and quantitative analysis of how all the components of its chosen biological system interact functionally over time. Model organisms (uni- or multicellular), and model cell populations (e.g. immune cells, skin cells, liver etc) are currently providing the best examples for Systems Biology research, using both discovery-based and hypothesis-based approaches. New directions in SB research are opening up opportunities to study interactions of organ systems and even populations in plants and animals, thus promising new advances in medicine, ecological management, the food industry and animal husbandry.

Systems Biology is now at a similar stage to Molecular Biology in the late '60s. It was then that the EMBL came into being as the first major infrastructure of the Life Sciences in Europe. EMBL succeeded beyond expectations by becoming a new type of institution, with stable funding, well-equipped headquarters of a reasonable size, but also several outstations, linked into a distributed but integrated, Hub and Spoke entity. A comparable RI is needed and intended for Systems Biology.

### 4.2.3 Immature Proposals

The proposals identified as being immature did not meet the criteria of major pan-European research. Some of these reasons to reject the proposals were in common to all proposals and others were very specific. In general they had too narrow a scope. In most of the cases a coherent management structure was missing.

**RU05 EurlMon – European Immune Monitoring Platform**
Submitted by the ESFRI delegation of Germany

The rationale for this proposal is to provide an 'immune monitoring' service which could help to develop vaccines. This is a laudable goal given the hardship of infectious diseases globally. The aspiration of coordinating efforts to expedite sharing of information, technologies, and samples and to develop new assays (such as biomarkers) is meritorious. Many groups working in vaccine development do so with very little, and poorly coordinated, infrastructural support. Insofar as this proposal seeks to address this big issue, it would be a welcomed improvement. The scientific field itself was considered as being very important for future research in the Life Sciences, but the proposal did not demonstrate maturity and did not meet the standards inclusion in the update of the ESFRI RM.

The BMS RWG recommends the scientific coordinator of this proposal to apply for appropriate calls within FP 7 to get support to develop the ideas to a pan-European infrastructure.

**RU18 EUSHAPE, European Standardisation and Harmonisation Platform for Bio-Medical Research**
Submitted by the ESFRI delegation of Germany

The essence of this proposal is to generate a new communication platform as an interactive infrastructure for investigators engaged in biomedical research. It is a very ambitious undertaking by aspiring to have a central harmonised data-set with outstanding communication options, and fixed specifications for bio-bank materials and a central source to address ethical issues. The RI plans to serve every area of expertise and to be a resource for industry as well as academic interests. If successful this would make Europe a more attractive space in which to do bio-medical research for industry and academics alike. In general, standardisation and improving accessibility to pan-European research data has the potential to deliver the research success in biomedical research.

The BMS RWG recommends the scientific coordinator of this proposal to strengthen the cooperation with the already existing RIs (BBMRI, EATRIS and ECRIN), which certainly require such a platform for their work.

**RU30 ASSA, Advanced sustainable sea-based Aquaculture**
Submitted by the ESFRI delegation of Norway

This proposal has been sent to the ENV RWG as leading RWG by the ESFRI Executive Board (EB) and not to the BMS RWG. Shortly before the BMS Expert Group meeting, January 14th 2008 in Berlin, the Norwegian ESFRI delegation asked the EB to also ask the BMS RWG to evaluate this proposal. BMS RWG agreed to give a statement and recommendation on ASSA.

The objective of this proposal is to improve fish farming methods in order to deal with the increased needs for fish in the near future. The BMS RWG came to the conclusion, that the research aspect in ASSA is limited and that the pan-European dimension is missing. The BMS RWG recommended that the ENV RWG should not recommend the proposal for the inclusion on the Update of the ESFRI RM because of the weakness of the research component and the fact that the proposed RI received support from only one country.

### 4.2.4 Proposals of other RWGs

The BMS RWG decided at its 10th Meeting in December 2007 that it had no expertise to evaluate RU 23, 25 and 32, which were primarily send to the ENV RWG. The ENV RWG was informed of this decision. As described below the three proposals were out of the scope of the BMS RWG.

**RU 23 EURAT; European Facility for Atmospheric Research**
Submitted by the ESFRI delegation of Italy

The main goal of this proposal is the observation of the atmospheric system. Thereby parameters like cloud structure, radiation fluxes, rainfall, water vapour, aerosols and other physical parameters will be measured and the data stored in databases. This topic fully fits to the field of environmental monitoring and the BMS RWG has no expertise in this field. Certainly climate changes will have an impact on crop growth and probably increase the spread of diseases, but these points are secondary within the proposal and the main topic itself is "measurement/ monitoring".

**RU 25 FASOF; Free-Air Sites for Ozone Fumigation (FASOF) for a scientifically-sound legislation to protect European vegetation against ozone**
Submitted by the ESFRI delegation of Italy

FASOF is dealing with the influence of atmospheric ozone on vegetation and aims to enhance transnational cooperation in the field of environmental protection. The BMS RWG decided that there were few points of contact between the BMS topics and this proposal, because the proposal focuses on environmental issues.

**RU 32 ANNAEE European Infrastructure for the Analysis and Experimentation on Ecosystems (France)**
Submitted by the ESFRI delegation of France

This proposal was an emerging proposal of the ESFRI RM 2006, covering the field of earth system research, and developing three mentioned platforms on long term monitoring ecosystems in conjunction with measurements of environmental fluxes to atmosphere and hydrosphere, analysing the physiology of ecosystems and database construction.

BMS RWG decided to leave the evaluation to ENV RWG because the proposal was clearly out of its scope.

### 4.3 Proposal Templates

#### 4.3.1 Mature Proposals

| *1. Descriptive title.* |
|---|
| **EU-OPENSCREEN**<br>**European Infrastructure of Open Screening Platforms for Chemical Biology** |
| ***2. Synthesis description of the new RI (or major upgrade) and S&T fields involved at Pan EU level in its use.*** |
| **"Chemical Biology", the systematic use of chemistry to explore biology, provides unique means for unravelling complex biological processes.** Its efficacy and impact largely depends on the availability of a diverse and well-designed compound collection, the availability of modern advanced screening technologies, chemistry resources, special cell collections, and a comprehensive database and computing capacities. However, the required infrastructure exceeds the capabilities of individual institutions or even countries; therefore it is necessary to organise and implement the essential features on a large scale at the European level.<br>**EU-OPENSCREEN is an open-access infrastructure for the development of bioactive small molecules. It includes a large collection of diverse compounds (at least 0.5 million), high throughput screening (HTS) centres, hit optimization facilities, and a publicly accessible database combining screening results, assay protocols, and chemical information. The integrated infrastructure will meet the needs for new bioactive compounds in all fields of life sciences (human and veterinary medicine, systems biology, biotechnology, agriculture, nutrition, etc.).** In the field of biomedicine, small molecules are essential for elucidating disease-relevant biological mechanisms. In this way, the infrastructure will also uncover new target classes, e.g. by exploring protein-protein interactions. In systems biology, bioactive compounds are used for perturbing complex biological networks to test mathematical models. In the areas of agriculture and nutrition, the study of metabolic pathways by means of small molecules will help to create plants with higher concentrations of desired metabolites or with a higher tolerance against diseases and other stress factors. Furthermore, small molecules may be used, for example, in biotechnology and regenerative medicine to functionalize surfaces. The European research community will benefit further from EU-OPENSCREEN through activities aiming at the exchange of assay systems and cell lines, the definition of common standards, and joint training measures.<br>**EU-OPENSCREEN brings together chemical and biological expertise** to overcome the fragmentation of European research in the field of Chemical Biology. Through the transnational and coordinated activities of EU-OPENSCREEN a substantially accelerated generation of knowledge on the bioactivities of chemicals as well as on the responses of biological systems will be achieved. European researchers from academia will obtain access to the most advanced screening technologies that are currently only available in an industrial environment.<br>**The new infrastructure will stimulate industrial research** by helping to define new targets and by carrying high-risk projects one step further before they are accepted by the pharmaceutical industry. It will, furthermore, train scientists and provide invaluable data on protein-ligand interactions. |

***3. Science case: scientific area(s) and potential and/or explicit users, how the new RI will fit into the existing and future landscape of Research and of existing RI's, at EU and World level.***

**Small molecules serve as unique biochemical tools to study protein function through dosage-, time- and spatially controlled perturbations of biological systems.** It would be highly desirable to identify a specific small molecule agonist or antagonist for each function of a protein. EU-OPENSCREEN thus aims at complementing the tools and technologies of molecular biology such as animal models, mutagenesis, antisense technologies, RNAi, or aptamers. However, we are currently far from adequately covering the wide variety of targets that have emerged from genome research. Chemical Biology addresses this deficit with a large-scale effort to develop new bioactive agents.

Nearly all areas of life sciences will profit from the availability of molecular probes in the manner described above. In **medicine**, pharmacological interventions are an essential feature of basic research since centuries. Originally, natural compounds were used, which are nowadays supplemented by synthetic compounds. Often, a variety of similar compounds is available which helps to distinguish the action of subtypes of proteins, an eminent challenge in investigations on the level of cells or organisms. The importance of small molecules in medical research is displayed, for example, in the appearance of the kinase inhibitor staurosporine in more than 2,000 research papers from the years 2000-2005. Currently, only few compounds have a similar status, but it is evident that this needs to be increased dramatically for the benefit of research in all biomedical areas.

In the context of **agriculture** and **nutrition**, novel small molecules will help in understanding metabolic pathways, with the aim to create plants containing a higher concentration of desired metabolites or which have an improved resistance against stress factors. This includes a higher tolerance against unfavourable environmental conditions such as dry habitats, especially important in view of climate change and increasing water shortages. A higher tolerance against plant diseases would be another highly desirable achievement, as the resulting reduction of herbicides, pesticides, and fungicides would benefit the farmer (lower costs), the agricultural personnel (less exposure to harmful substances), the consumer (less intake of harmful substances), and the environment.

A major goal of current life sciences is to obtain a systemic view of life. This implies a change of focus from single molecules to biological networks at different levels of complexity. Discovering and analysing these networks requires perturbing the activity of the involved molecular components – in most cases proteins – through genetic or chemical means, the latter corresponding to pharmacological intervention. In **Systems Biology** the perturbation of individual interactions or catalytic functions of a protein is an important part of the methodology, and Chemical Biology extends the method portfolio beyond the capabilities of knock-out techniques. It is this area, which demands for 'one agonist or antagonist for each protein function', which is intended to be satisfied by this infrastructure. In **biotechnology**, highly specific small molecules can be used for affinity purification, especially of individual protein complexes, for functionalizing medically relevant surfaces, for stabilizing protein preparations, for enabling crystallization etc. Taken together, there are many fields in current life sciences and even some in material sciences that will profit from a Chemical Biology infrastructure.

**EU-OPENSCREEN will be used by researchers from Universities and research institutes, who have either only limited in-house facilities or no access at all to such an infrastructure, thereby satisfying an unmet demand in the field of life sciences.**

It complements the goals of other European life science initiatives. The closest of these is ***ProteomeBinders*** (European Resource for Ligand Binders, http://www.proteomebinders.org), which aims to establish a repository of binding molecules for at least 100,000 human target proteins to provide tools for detection, quantification and characterisation of these proteins.

This proteome research repository will be primarily built on antibodies and other protein receptors, but intends to include small molecules as well. Thus, there will be a close interaction between EU-OPENSCREEN and ProteomeBinders to exchange results and selected compounds for the ProteomeBinders repository. However, the working principles of the two infrastructures are very distinct, being on one side the screening platforms that will carry out experimental work and on the other side a repository with reagents to be distributed. ***Instruct*** (Integrated Structural Biology Infrastructure for Europe, http://www.instruct-fp7.eu/) will maintain a set of core technologies (e.g. protein production, NMR, crystallography, different forms of microscopy), and combine this with a specific biological focus that will drive the development of technological and methodological expertise, notably for the analysis of functional complexes.

This infrastructure will be ideally complemented by EU-OPENSCREEN, since small molecules may promote crystallization and stabilize complexes, and EU-OPENSCREEN will profit through the opportunity for structure-based design of small molecules. Considering Chemical Biology as part of the life science pipeline, EU-OPENSCREEN will be connected through its output – bioactive compounds – and through the required input – cell lines for assays, etc – to initiatives providing cell or animal models like ***Infrafrontier*** (European infrastructure for phenotyping and archiving of model mammalian genomes, http://www.infrafrontier.eu/) and ***BBMRI*** (Biobanking and Biomolecular Resources Research Infrastructure, http://www.bbmri.eu/). An exchange of materials and information with the two initiatives would create mutual benefits. The collaboration with various agricultural Technology Platforms and projects will be established through ***Agri-Net*** (EU-funded Agricultural portal, http://ec.europa.eu/research/agriculture/).

The Chemical Biology database, a very important feature of EU-OPENSCREEN, could be linked to ***ELIXIR*** (European Life Science Infrastructure for Biological Information, http://www.elixir-europe.org/) and supplement the latter's databases. In case of therapeutically relevant compounds, interactions with networks like ***EATRIS*** (European Advanced Translational Research Infrastructure for Medicine, http://www.eatris.eu/) and ***ECRIN*** (European Clinical Research Infrastructures Network, http://www.ecrin.org/) will ensure the availability of appropriate follow-up research. In particular, GLP-production of small molecules *via* EATRIS would be an important perspective in medically interesting cases of success.

EU-OPENSCREEN is essential for European scientists to stay at the forefront of research in the life sciences. It will fulfil similar needs for Europe as does the ***Molecular Library Initiative, MLI*** (http://mli.nih.gov/mli/) of the National Institutes of Health (NIH) road map for the USA (Austin et al. 2004 Science 32006, 1138). Both initiatives share the concept of combining screening centres, small molecule libraries, and a central database. The MLI currently has a library size of 100,000 compounds. Nevertheless both concepts are distinct in several aspects. EU-OPENSCREEN will realise a close integration of chemistry resources for hit optimisation and tool development and thus establishes a work-flow going far beyond the identification of hits. A further difference is the handling of IP issues, with the MLI imposing the full disclosure of all structural and activity data in the database (PubChem). As a result, bioassays and proprietary compounds with commercial potential are not deposited in the PubChem database. EU-OPENSCREEN avoids this limitation by distinguishing between public and non-public areas, the latter being suitable for deposition of e.g. proprietary compounds and novel assays prior to patenting.

### *4. Technical case: summary of results (technical specifications) of conceptual and/or technical design studies.*

**The infrastructure will be composed of integrated screening platforms hosting high-throughput methodologies, a central compound management, and, as a key element, a database.** Common standards will be established for efficient transfer of materials and procedures. There will be a restricted number of screening centres with large compound collections, applying various methodologies and operating at a high degree of automation. During the Preparatory Phase (PP) the design of the infrastructure will be discussed in further detail and

specifications will be elaborated. Technical challenges are the creation of a large compound collection (> 0.5 million substances) and the establishment of a high degree of automation at the major sites.

The compound collection will be designed for the needs of academic screening. It should be diverse and contain well-chosen subsets for fragment-based screening, for certain protein families, or of natural products, etc. Of course, maintenance, quality control and distribution are not trivial, and appropriate procedures need to be established. The major screening centres will be highly integrated, host copies of the compound collection, and each will offer special screens corresponding to their expertise.

During the PP, a survey is required for specifying the needs of the scientific community with respect to types of screens and expertises concerning protein classes and screening technologies present at various sites in Europe. The elaboration of standards, data formats and the minimum information content of an assay constitute also important challenges. In addition large resources are required for service chemistry to optimize hits. During the PP a survey of the various possibilities for organising hit optimisation will be performed. Of highest importance is the database which will be designed for the needs of academic screening and ligand development.

In the long run, it will become a treasure for those researchers who develop bioactive compounds, programs for drug design etc. Further studies during the PP will include a survey of protein production facilities (existing, for example, within INSTRUCT) and of the experimental basis with respect to cell lines and animal models, including an interface to other European initiatives. These discussions will include particularly follow-up research like testing compounds on animal models, and approaches to solving ADMET-problems.

The main elements of EU-OPENSCREEN will be

- A central compound collection comprising at least 0.5 million chemical entities, including proprietary compounds, with appropriate storage and distribution systems. Focussed subsets of the collection for various biological targets will be included.
- Screening centres with high-end equipment, such as automated microscopes for cell assays or systems for automated capillary electrophoresis.
- Facilities for chemical optimisation of hits and development capacities for new types of assays.
- A central ADMET facility hosting appropriate cell lines and cell import systems.
- A central database combining screening results, assay protocols, and chemical information (European Chemical Biology Database, ECBD). The database could be linked to existing genomic and proteomic databases through ELIXIR (http://www.elixir-europe.org/), the European Life Science Infrastructure for Biological Information, an initiative coordinated by the European Bioinformatics Institute (EBI).
- An efficient and speedy evaluation of incoming applications will be organised by the central management office, involving both external and internal experts in the field of Chemical Biology.

It is envisaged to create a legal entity, such as e.g. a European Interest Group (EIG), in order to facilitate the interaction of the stakeholders involved and their cooperation with the external users. EU-OPENSCREEN membership will be open to all European organisations involved in Chemical Biology. A central research and training facility will be established, including a central management office.

**Rules for the handling of Intellectual Property (IP) related issues have to be defined.** The general approach will be to set up a flexible framework for IP issues in order to allow for a protection of knowledge before including the results in the database.

EU-OPENSCREEN's mission to create an open platform for the enhancement of the exploitation of chemical entities for studying biological processes is not encouraged by patent law, since a lack of affordable early options for IP protection inhibits disclosure of research discoveries and their deposition in an open database. In view of this situation, the NIH, which funds a similar large initiative (MLI and PubChem database), follows a policy which does oblige deposition of research results from its funded projects in PubChem, but rather discourages patenting in order not to prevent the widest use of these tools as a "community resource".

It is expected that researchers in the public and private sectors will use the MLI substances as proof-of-concept compounds and solely as starting points to produce chemical analogues with improved properties which will allow the patenting of follow-up inventions. This policy, however, disregards to some extent interests and needs of industry and academia. EU-OPENSCREEN will stimulate and support activities towards advancement of the current patenting situation. Activities should particularly address the needs of large data repositories and open collaborative networks, which require a balance between rapid knowledge sharing on the one hand and protection and exploitation activities on the other hand.

***5. e-infrastructure: what does the new RI require as far as e-infrastructure? How is it integrated with the existing EU e-infrastructure (e.g. Geant, grid, digital repositories).***

A key element of EU-OPENSCREEN will be a common database (European Chemical Biology Database, ECBD), where all data generated are collected and made available to the public. It could be linked to existing genomic and proteomic databases through ELIXIR, the European Life Science Infrastructure for Biological Information (http://www.elixir-europe.org/), an initiative coordinated by the European Bioinformatics Institute (EBI). Links to DRIVER (Digital Repository Infrastructure for European Research, http://www.driver-repository.eu/) could be established as well. The European Chemical Biology Database established within EU-OPENSCREEN will become an extremely valuable treasure for e.g. biotechnology, agriculture and future drug development in Europe.

***6. Other expected socio-economic impacts: development of new technologies, effects on training, involvement of industries, local impact, other.***

**The broad interdisciplinary Chemical Biology approach of EU-OPENSCREEN (covering all areas of molecular life sciences) brings together chemists, engineers, informaticians and biologists and creates numerous opportunities for innovation and commerce.** Bioactive chemical compounds are not only the most common form of medical therapies, they also are of great relevance for agriculture, nutrition and biotechnology. Thus EU-OPENSCREEN opens new paths for research in the post-genomic era and its most direct translation from basic science into improved quality of life. All life-science-based activities will therefore profit from EU-OPENSCREEN. In particular, EU-OPENSCREEN will focus on high-risk research, which precedes commercial development of innovative bioactive compounds. **Unlike commercial screening platforms and pharmaceutical industry, it will mainly use non-validated targets and identify entire new target classes, which will dramatically broaden the basis for the commercial developments of bioactive compounds.** In addition, the infrastructure will establish a comprehensive database, which exceeds by far the information provided by commercial screening platforms and therefore represents an entirely new resource, currently not available to European researchers. Thus the new infrastructure will not compete with commercial screening platforms, whose focus is on drug development, using mainly validated targets. In the contrary, it will feed the development pipelines of the European industry. It will promote competitiveness, growth and jobs, economic and social cohesion: all essential components of the overarching objective of sustainable development, as laid out in the Lisbon Agenda.The initiative is firmly supported by various European companies.

**For the first time, the distributed infrastructure will offer European researchers from**

**academia access to the most advanced screening technology that is currently only available in pharmaceutical industry** and which underlies many restrictions (e.g. financial restrictions and restrictions regarding IP). In addition, the interdisciplinary research will lead to novel screening technologies and supporting test systems which are initially only available in the academic environment. Moreover, it will to a great extend bioprofile proprietary compounds provided by chemists from Europe. Finally, the inherent training aspect is intensified through the establishment of links between Universities and research institutes on the one hand and SMEs and large companies on the other hand. Thus, EU-OPENSCREEN activities exceed by far those of commercially available screening services.

**The initiative will contribute to better protection and improvement of health, have an impact on farming and food production, and therewith encourages and facilitates innovation, research, and development in pharmaceutical, biotechnology, healthcare and agricultural areas.**
The research-based biopharmaceutical, food and agricultural industry is of great importance for European citizens as well as for the economic future of Europe. However, the number of new chemical entities (NCEs) reaching the market has been decreasing in the past years, whereas industrial investment in R&D has been constantly increasing.
EU-OPENSCREEN will target these challenges because it will

- broaden the basis for the commercial development of bioactive compounds,
- bridge the gap between academic research projects and the commercial development of bioactive compounds,
- secure IP from academic projects for commercialisation,
- provide efficient bio-profiling of novel synthetic compounds vs. a broad variety of protein targets thus allowing rapid identification of NCEs,
- elucidate the underlying mechanisms of complex biological pathways and therewith boost scientific research and development in the all fields of life sciences, and
- promote the availability of safe and efficacious chemical products for so far unmet needs in medicine, nutrition and agriculture.

EU-OPENSCREEN will assure that the scientific treasures of European research in the field of Chemical Biology are optimally exploited for the benefits of research and society.

### *7. Commitments / maturity: which States / Organizations have demonstrated interest / commitment in supporting and/or funding the proposal?*

In recent years the need for a coordinated Chemical Biology approach already lead to the development of several regional initiatives e.g. in France, Germany, Scandinavia, Spain and the United Kingdom. In several further countries such as Austria, the Czech Republic, Israel, Italy, Poland, and Switzerland institutes with Chemical Biology expertise have evolved. However, the capacities of these emerging, local screening platforms are far from being able to meet the demand in a European context.

**EU-OPENSCREEN will overcome these limitations** by setting up an integrated infrastructure for interdisciplinary Chemical Biology projects in Europe. Thereby it will provide a central resource for discoveries and innovation in Chemical Biology and related fields.

**In the following a non-exhaustive list of organisations/initiatives involved in Chemical Biology is given. Stakeholders from all countries listed below have declared their commitment to EU-OPENSCREEN. Further organisations or countries may want to become involved. This will be explored before and during the Preparatory Phase following defined extension criteria.**

- **Austria**: The Research Center for Molecular Medicine (CeMM) of the Austrian Academy of Sciences (http://www.cemm.at). The scientific director, Prof. Giulio Superti-Furga, is dedicated to ‘integrative systems biology’ and wants to use small molecules for pull-down of protein complexes. He supports strongly the establishment of an Austrian plat-

form for Chemical Biology.

- **Czech Republic**: The Institute of Molecular Genetics (IMG), Prague (http://www.img.cas.cz/) has numerous groups working on proteins with Chemical Biology methods including phenotypic screening assays.
- **France**: Several regional screening initiatives have been started, and the Institut Pasteur in Paris has developed into a major player. The French Screening Network includes centres in Strasbourg, Saclay, Roscoff, Toulouse, and Grenoble (http://ifr85.u-strasbg.fr/project/rnc/). In addition, CNRS and others have established a French National Chemical Library (http://chimiotheque-nationale.enscm.fr/) which would be a major asset of the ESFRI consortium. *(Already funded by national grants.)*
- **Germany**: ChemBioNet – Resource Network to Support Chemical Biology Research in Academia (http://www.chembionet.info/); founding members are FMP Berlin (Prof. Walter Rosenthal), HZI Braunschweig (Dr. Ronald Frank) and MDC Berlin (Prof. Walter Birchmeier); the central screening platform and the compound collections are located at FMP Berlin. *(Already funded by national grants.)*
- **Israel**: Prof. Alexander Levitzki, The Hebrew University of Jerusalem (http://biolchem.huji.ac.il/levitzki/levitzki.html), is an outstanding protagonist of Chemical Biology, representing the community from Israel. He is an expert in the development of kinase inhibitors with a long track record in industrial applications.
- **Italy**: At the University of Milan (http://users.unimi.it/dpcorind/en/) the CISI Center of biomolecular interdisciplinary studies is located. Headed by Prof. Carlo Scolastico the center offers expertise on high throughput synthesis, combinatorial chemistry, molecular modelling and chemical analysis for chemical biology projects.
- **Poland**: Contacts to the polish community are established through Prof. Piotr Zielenkiewicz, who is director of the Institute of Biochemistry & Biophysics, Polish Academy of Sciences, and heads the Department of Bioinformatics (http://www.ibb.waw.pl/staff/__bioinf.html). He is interested in the modeling of metabolic pathways and molecular crowding, adding a systems biology component.
- **Norway and Sweden**: The Scandinavian Chemical Biology Platform maintained by both countries covers all aspects of Chemical Biology; key players are University of Oslo (Prof. Kjetil Tasken, http://www.biotek.uio.no/research_groups/tasken_group.html) and Umeå University (Profs. Mikael Elofsson, F. Almkvist, A. Linusson). *(Already funded by national grants.)*
- **Spain**: The Spanish Drug Discovery Platform (http://www.pcb.ub.es/drugdiscovery) is supported by groups in the Barcelona Science Park, the screening platform at Santiago de Compostela (http://www.usc.es/) and other groups in Spain. It includes a national compound collection, the Spanish ChemBioBank, located in Barcelona. *(Already funded by national grants.)*
- **Switzerland**: The Swiss community is represented by the EPFL (http://bsf.epfl.ch/) screening facility which covers all important aspects for the development of bioactive compounds. It is headed by Dr. Gerardo Turcatti who has valuable industrial experience in drug development.
- **United Kingdom**: Chemical Biology in the UK is strongly supported by the Wellcome Trust which has established several major screening facilities. Dr. Julie Frearson, University of Dundee (http://www.lifesci.dundee.ac.uk/) is head of probably the largest screening unit focusing on tropical diseases and represents this community. In Cambridge small molecule screening has been linked to protein crystallisation (http://www.bioc.cam.ac.uk/uto/blundell.html). *(Already funded by national grants.)*

**An important feature of the proposed infrastructure is that it is open to further interested parties and emerging screening centres.**

The establishment of EU-OPENSCREEN requires a 2.5 years Preparatory Phase. The costs for operation include finances for maintaining the compound library, for addition of new compounds, for maintenance of the HTS machinery, and for development of novel screening technologies, plus personnel costs. A sum of 40 million Euros as initial investments for the various sites and the central facility will be required, and running costs per year in the range of 40 million Euros, including personnel and consumables.

| ***8. Costs for construction, operation and decommissioning, indications on project financing. Give budget info in Mio €*** | | | |
|---|---|---|---|
| Total preparatory cost<br><br>4-5 Mio € | Total construction cost<br><br>40 Mio € | Operation cost /year<br><br>40 Mio € | Decommissioning cost<br><br>*not applicable* |
| (of which already spent or committed)<br><br>- | (specify contributions committed or indicated by possible funders)<br>- | (specify contributions by possible funders)<br><br>- | (possible funders)<br><br>*not applicable* |

| ***9. Timetable for construction, operation and decommissioning (half page, with references/links)with duration and possible starting dates.*** | | | |
|---|---|---|---|
| Preparatory phase<br>2.5 years | Construction phase<br>1.0 year | Operation<br>>10 years | Decommissioning<br>- |

***10. Reference: Person who has submitted the proposal, and will follow up in ESFRI***

Contact:
Prof. Dr. Walter Rosenthal, MD
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***1. Descriptive title, and information on the ESFRI delegation submitting the proposal (or one of the member of EIROForum)***

**Euro-BioImaging**
**Euro**pean **Bio**medical **Imaging** Infrastructure - from Molecule to Patient

***2. Synthesis description of the new RI (or major upgrade) and S&T fields involved at Pan EU level in its use. Add links to relevant data/web pages***

Research in and application of, biomolecular and biomedical imaging is progressing rapidly and increasingly this growth is in a multidisciplinary manner. Innovative imaging techniques are key tools for all life scientists to understand living systems at both the molecular and the physiological level, from biological model systems to patients. Imaging technologies are core disciplines of tomorrow's biology and medicine, and represent essential new research infrastructure for the life sciences. Now is the time to provide broad access to state-of-the-art and new emerging imaging technologies to the European scientific community, to strengthen research and training in imaging and to ensure European leadership in this competitive field.

Euro-BioImaging brings together key research areas in the imaging field stretching from basic biological imaging with advanced light microscopy, to the clinical and epidemiological level with medical imaging. Euro-BioImaging will address the imaging requirements of both basic and medical imaging communities by creating a coordinated and harmonised plan for infrastructure deployment in Europe.

Euro-BioImaging will be organized into strongly interlinked *nodes*, each focused on complementary imaging technologies addressing different aspects of biology, physiology and pathophysiology. Nodes will be newly constructed or undergo major upgrades in order to devote a significant part of their capacity to external users. In this manner, the infrastructures will provide access to imaging technologies across the full scale of biological and medical applications in an integrated manner, allowing translation of new developments from laboratory to clinical use.

Advanced microscopy and medical imaging have common goals in several areas, which will be served by integrated nodes commonly used by both communities. In addition to these common domains, both communities also have specific needs that will be served by dedicated nodes.
Euro-BioImaging nodes will be supported by associate centres in each technology area. Associate centres will develop specialized imaging technology and transfer it to the infrastructure nodes to provide general access. In addition to associate centres, the nodes will be embedded in a wide network of European imaging facilities in almost each ESFRI member state already organized in the European Light Microscopy Initiative and Training network (ELMI, http://cci.sahlgrenska.gu.se/ELMI/ and EAMNET, http://www.embl.de/eamnet/) and the European Institute for Biomedical Imaging Research (EIBIR, http://www.eibir.org/).

***3. Science case: scientific area(s) and potential and/or explicit users, how the new RI will fit into the existing and future landscape of Research and of existing RI's, at EU and World level***

Euro-BioImaging infrastructures will meet the challenge for access to state of the art equipment as well as provide training and continue the development of imaging technologies. As imaging methods are grouped around different scales of biological organization, from the molecule to the human organism, Euro-BioImaging nodes will be complementary, rather than redundant, to allow focused use of resources in dedicated centres of excellence. The over-arching Euro-BioImaging goal is to provide research infrastructures for multidisciplinary projects by combining biologists, chemists, physicists, bioengineers, computer scientists, imaging technologists and clinicians in order to deliver world class methods for biological and medical applications.

The nodes listed below are the core that will set a pan-European foundation for Euro-BioImaging. In the preparatory phase additional topics will be evaluated, based on the needs of the community. It is expected that in each community, advanced light microscopy (ALM) and medical imaging (MI), at least one additional node will become necessary. For example, Raman spectroscopy or nanotechnology are two emerging areas that are becoming increasingly relevant for biomedical imaging and may merit formation of an additional node.

**Common Nodes**

*Large scale image processing and computing.* Will provide access to quantitative image processing methods and develop concepts for computing infrastructure for large scale image data volumes generated by present and future biomedical imaging technologies. Computing is not limited to raw signal processing but will include modelling of in vivo processes. It will be connected to the European high speed data network and grid computing initiatives. Computational tools will be essential towards the development of imaging biomarkers, which will have a large impact on better understanding the mechanisms of disease.

*Databases for quantitative biomedical imaging.* Will provide access to database models for quantitative imaging data. For large scale quantitative datasets, central digital repositories will be developed that are essential for imaging phenotypes of multiple diseases as well as personalized therapeutic approaches. This node will be intimately linked and synergistic with the ESFRI initiative ELIXIR and other databases (ACRIN, BIOBANK). This node will also develop solutions for data storage and retrieval and for the transfer of large amounts of data.

*Imaging of tissues and animal models:* Will provide access to methods for imaging tissue function from animal brains to whole animal models. Key technologies will include multiphoton live imaging, applying light microscopy techniques to animal imaging, ultra-high-field animal MRI and hybrid molecular imaging technologies including PET and SPECT combined with CT or MRI. In addition, new approaches in intra-vital imaging such as novel miniaturized objectives and microchip lasers will be explored.

**Advanced microscopy nodes**

Advanced light microscopy is instrumental to reach the ultimate goal of biological imaging, to visualize single biomolecules and their functions and interactions within the context of live biological systems. The specific nodes will provide the following key technologies.

*Superresolution light microscopy*. This node will provide access to methods that improve the spatial (and also temporal) resolution of light microscopy imaging with an emphasis on technologies applicable for biological applications and in live specimen. Key technologies will include stimulated emission depletion (STED), photoactivation localization microscopy (PALM) as well as the use of structured illumination.

*Functional imaging of live cells.* This node will provide access to methods that visualize molecular function in live cells. Key technologies will include fluorescence lifetime imaging (FLIM), fluorescence (cross) correlation spectroscopy (FC[C]S), photoactivation and photobleaching (PA, FRAP), single molecule imaging, and novel fluorescent reporters of biochemical reactions. It will be linked to the ESFRI initiative INSTRUCT.

*Correlative light and electron microscopy.* In this node it will be possible to combine dynamic functional assays in live cells directly with high resolution 3D morphology at molecular resolution by EM (cryo) tomography. This node will be intimately linked to EM activities in INSTRUCT.

*High throughput microscopy for systems biology.* This node will contribute to systems biology and rational drug development by providing access to automation and high throughput in advanced light microscopy methods including ultra high content screening of genome level systematic perturbations of biological systems such as RNA interference over-expression or small molecule screening.

**Medical imaging nodes**

Euro-BioImaging will provide an infrastructure in medical imaging through dedicated biomedical imaging nodes focusing on the following key areas;

*Design and testing of novel agents and probes.* This node will provide access to new imaging agents that can improve visualization of pathologies and cellular processes. Nanotechnology is

an important aspect of this node that will allow users to apply quantum dots, nanoparticles, nanoshells, microbubbles, radio-labelled contrast materials, and smart imaging agents that are multifunctional or activatible.
*Population based imaging:* Structural and functional changes occur in the years preceding clinical onset of disease. This node will support imaging in large, prospective epidemiological studies in unselected populations. This enables identification of imaging biomarkers and risk factors of pre-symptomatic disease as imaging phenotypes play an essential role in the early detection of people at risk.
*Clinical trials in imaging.* New methods in medical imaging are often adopted without sufficient scientific proof and larger clinical trials with appropriate end-points to prove the benefits should be planned. This Euro-BioImaging node will create the infrastructure for planning, conducting and monitoring large clinical multi-centre trials in diagnostic imaging and image-guided interventions.
*Minimally invasive image-guided interventions.* Will give access and disseminate optimized tools for application in minimally invasive image-guided interventions. Providing detailed 3D and 4D information on the anatomy and function acquired prior to the intervention will improve navigation and reduce intra-operative radiation and intervention time. Image guidance will also be applied to stem cell therapy on many levels.

### *4. Technical case: summary of results (technical specifications) of conceptual and/or technical design studies*

The vision of Euro-BioImaging is to provide the technology to be able to image every macromolecule in its natural environment. Imaging from cells to model organisms to humans is the long term vision that requires multidisciplinary innovation. Once techniques have been developed, anything visualised at a molecular / cellular level could be used in a therapeutic approach, to help diagnosis, guide therapy and design drugs. Once better resolution and enhanced image processing is available, imaging modes across different scales of biological organization will become quantitative, a key prerequisite for systems biology and the development of imaging biomarkers.

Euro-BioImaging will be equipped with the most advanced instrumentation for a wide range of imaging modalities and it will be endowed with the capability of developing suitable molecular probes as well as the proper cellular and animal models to study a given pathology. Euro-BioImaging nodes will therefore not only provide access to imaging technologies but at the same time ensure that these infrastructures remain at the cutting edge of technological development. It will be important to continuously keep developing new imaging methods and instruments, which can overcome current technical challenges, associated with the resolution (space, time) or sensitivity. Due to the nature of modern imaging methods, these developments require the combination of interdisciplinary expertise from biology, medicine, physics, chemistry, engineering and computing, which can ideally be achieved at the integrated nodes that will be constructed by Euro-BioImaging. Euro-BioImaging infrastructures will be located at sites that have demonstrated excellence in each technology area and that have the capacity and commitment to establish an infrastructure that gives access to external users. Several of the identified partners have already demonstrated that they can provide efficient access to their technologies in the framework of scientific collaborations.

Euro-BioImaging will be linked to ELIXIR (European Life Sciences Infrastructure for Biological Information), INSTRUCT (Integrated Structural Biology Infrastructure for Europe), EATRIS (European Advanced Translational Research Infrastructure in Medicine) and to ECRIN (Network of Distributed Infrastructures for Clinical Trials). Euro-BioImaging will also be linked to the existing large scale physics facilities such as CERN or ultra-high field MR systems becoming available within NEUROSPIN to integrate new ideas for the development of novel, innovative imaging procedures and with the Bioinformatics resource infrastructures for accessing the most efficient procedures for handling the acquired imaging data.

***5. e-infrastructure: what does the new RI require as far as e-infrastructure? How is it integrated with the existing EU e-infrastructure (e.g. Geant, grid, digital repositories).***

e-infrastructure is an integral part of the Euro-BioImaging proposal and it will make extensive use of the existing e-infrastructures in Europe (GEANT, GRID). With the increasing automation of ever more complex experimental protocols, the amount of digital image data that is currently generated is growing exponentially. Single high throughput or high resolution imaging experiments can, for example, generate data volumes of multiple Terabytes. This will place substantial demands on data storage infrastructure at each node, but even more importantly requires Euro-BioImaging to make the tools available to process digital image data using high performance computing. Euro-BioImaging will meet this need through its node on *large scale image processing and computing* which will be linked to European GRID computing and high speed data network initiatives.

Furthermore, driven by the power of computerized image processing the data produced will be quantitative rather than qualitative to enable systems biology and imaging biomarkers. This means that comparison of data sets, and centralized repositories for rapid and machine readable retrieval, are a key emerging need in the imaging community. On one side this will be solved by establishing one node on *databases for quantitative biomedical imaging*. This node will be intimately linked to the ESFRI initiative ELIXIR. On the other side connecting large image databases with clinical and genetic information and developing intelligent data-mining algorithms will allow the extraction and establishment of new relations between genotypes and imaging phenotypes.

***6. Other expected socio-economic impacts: development of new technologies, effects on training, involvement of industries, local impact, other.***

Improved health care for European citizens will translate into economic advantages for the society, and the discovery of new products, new equipments, and new diagnostic and therapeutic procedures will represent important income for the institutions involved. The health care market is growing fast and the activities carried out within Euro-BioImaging are expected to yield a marked increase of the European IP in fields ranging from imaging methods to innovative diagnostic methods.

Euro-BioImaging will establish strong ties with European industry. Traditionally, European industry has held a worldwide leadership in the field of imaging technologies [Carl Zeiss (D), Leica Microsystems (D), Philips (NL), Siemens (D), Bayer-Schering (D), GE Health Care (UK), Bracco (I), Guerbet (F)]. Both ELMI and EIBIR Industry Panels already involve these leading companies and thus provide an ideal starting point for Euro-BioImaging to advance European leadership in development of imaging technologies. Nodes will cooperate closely with companies to apply new technologies to the needs of the biomedical imaging community. European companies will actively contribute to the development of technology and biological applications at Euro-BioImaging nodes, where a multidisciplinary environment and cutting edge research applications will be readily available. This will allow the industry partners to define new concepts faster and deliver prototypes closer to the final product, significantly increasing their competitiveness and generating added European value.

Euro-BioImaging will have a major impact on the training of European scientists. First, this will be done by training external users at the Euro-BioImaging nodes for the specific technologies they offer. This training will cover all aspects necessary to obtain conclusive data using the technology, ranging from specimen preparation to data collection and analysis. This will disseminate expert skills in the scientific community and ensure maximum return in the use of the advanced technologies. Second, Euro-BioImaging will provide training in new technologies to the existing local imaging facilities organized in EIBIR/ELMI. This “training of the trainers” will ensure that the needs of European scientists can be addressed at the closest possible physical

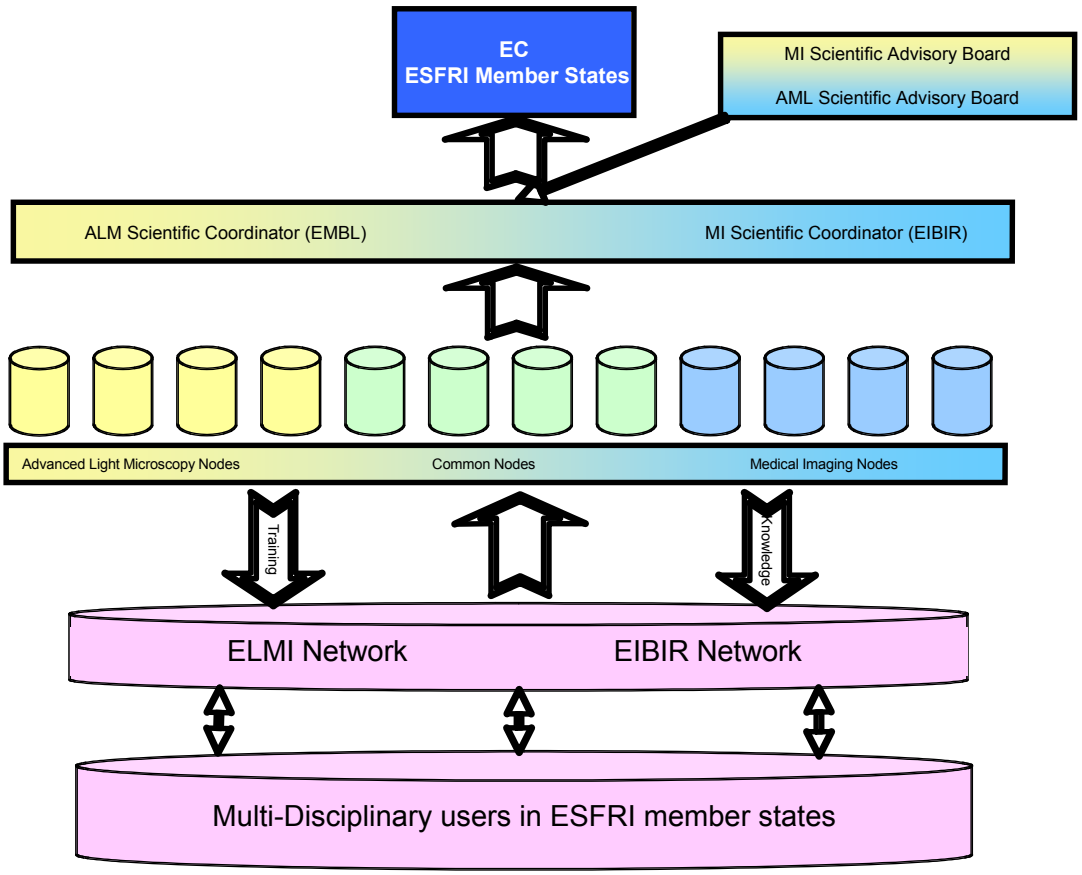
distance. Third, Euro-BioImaging will provide basic training in imaging technologies through the well established initiatives in ELMI, EAMNET and ESOR that have already made successful and widely recognised contributions to training and trans-national access.

Euro-BioImaging will consider itself a success once Europe has a world leading infrastructure in terms of both equipment and the critical mass required to develop, maintain and use it. A key measurement of success is the user satisfaction of those who access the infrastructure and receive the necessary training for its use. Processes will be established to obtain feedback on essential points and to implement corrective measures where necessary. Once Euro-BioImaging meets the needs of the user communities it will be considered a success.

### *7. Commitments / maturity: which States / Organizations have demonstrated interest / commitment in supporting and/or funding the proposal?*

In the present European context, the awareness of the need to organize long term imaging infrastructures for Europe is well known and expressed among the members of the imaging community. Many organisations and networks exist, but often focus on single aspects whereas Euro-BioImaging wishes to involve the widest possible range of disciplines and expertise. The ELMI/EAMNET and EIBIR networks will serve as a launching pad to guarantee the participation of the major actors in the field and final commitments will be obtained during the preparatory phase. The Euro-BioImaging project will be lead by two major imaging organisations, EMBL and EIBIR, both of which are ready to start the work immediately.
EMBL, the European Molecular Biology Laboratory, an intergovernmental organization with 20 member states, is prepared to take a global lead for the advanced light microscopy area of the Euro-BioImaging project. Dr. Jan Ellenberg, who coordinates the EMBL Centre for Molecular and Cellular Imaging, will serve as the scientific coordinator for the advanced light microscopy arm of Euro-BioImaging. EMBL is ideally suited as a coordinating organization for two reasons. First, EMBL has a demonstrated track record in successfully running several large European Research Infrastructures. Second EMBL is home of one of the largest advanced light microscopy core facility in Europe (ALMF, headed by Dr. Rainer Pepperkok), the only core facility in light microscopy that already provides regular access to outside users. In addition to the coordinating function, EMBL is ready to host the node on *high throughput microscopy for systems biology*, due to its demonstrated expertise in this area (MITOCHECK).
EIBIR, the European Institute for Biomedical Imaging Research, a non-profit limited liability company has been set up in 2006 with the aim to promote networking and cooperation in biomedical imaging within Europe. EIBIR has been identified as a crucial development for Biomedical Imaging in Europe in the recent strategic position paper of the European Medical Research Council of the ESF. The Medical Imaging area will therefore be led by Professor Gabriel P. Krestin, of Erasmus MC, University Medical Center Rotterdam, who was instrumental in the successful launch of EIBIR. EIBIR is the coordinating partner of a number of EC funded large scale projects related to cell imaging (ENCITE) and development of imaging biomarkers (HAMAM).

**Euro-BioImaging Interactions and Management structure**




In addition to EMBL and EIBIR, strong partners with demonstrated excellence in the respective technology and the capacity and commitment to host the different infrastructure nodes will be key to the success of Euro-BioImaging. Potential partners for many of the planned nodes have already been identified in different member states and several of them are ready to participate in Euro-BioImaging. Examples are Prof. Jerzy Duszynski of Nencki Institute in Warsaw (PL) (*imaging of tissues and whole animals)*; Prof. Judith Klumperman of the University of Utrecht (NL) (*correlative light and electron microscopy*); Prof. Michael Unser of the Ecole Polytechnique Federale de Lausanne in Lausanne (EPFL, CH) (*large scale image processing and computing*) and Dr. Wolfgang Huber of the European Bioinformatics Institute in Hinxton (UK) (*databases for quantitative biomedical imaging*), Prof. Silvio Aime of the Department of Chemistry of the University of Torino (*development and testing of novel agents and probes*), Prof. Wiro Niessen and Prof. Myriam Hunink of the Erasmus MC, University Medical Center Rotterdam (*population based imaging and clinical trials for imaging technology assess*ment), Prof. Fiona Gilbert of the University of Aberdeen (*clinical trials in oncology imaging*) Prof. Christian Herold and Prof. Johannes Lammer of the Medical University of Vienna (*image-guided interventions*).

Among the first tasks of the preparatory phase will be to consolidate the nodes and associate centres of Euro-BioImaging in a process open to additional partners and needs of the Biomedical Imaging community.

Particular attention will also be devoted to integrate the activities of Euro-BioImaging with the major European scientific associations and research initiatives in the field. Examples are projects such as European Network for Cell Imaging and Tracking Expertise (ENCITE) 3D vascu-

lar imaging (VASCAN), Molecular imaging (MOLIM), genome and its dynamic 3D structure in the cell (3DGENOME), membrane structure resolution (E-MeP), high throughput imaging to study mitosis (MITOCHECK) and nanotechnology (NANOMED) to name but a few. There are also 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 interact strongly with the proposed infrastructure.

***8. Costs for construction, operation and decommissioning, indications on project financing. Give budget info in Mio €***

One of the main goals of Euro-BioImaging is for Europe to maintain and extend its competitiveness in imaging technologies. The required investment is high and should be in addition to funds allocated to basic research and not part of it. The use of such an investment through a coordinated plan well integrated into the current and future European research landscape will have significant advantages. First, the investment can be more targeted so that the cutting edge technology is not duplicated unnecessarily in each member state. Second, the dissemination of know-how and technology to constantly update and improve the infrastructures will be more efficient. Third, it will facilitate the use of shared resources and standards (algorithms, data standards, compute processing power, databases).
Euro-BioImaging will be coordinated by two scientific coordinators supervised by an International Scientific Advisory Board. The implementation of Euro-BioImaging will take place in the three stages:
1. Preparatory phase. The main objectives are; to develop a funding plan for construction and operation, organize access and training, define the legal organisation for Euro-BioImaging, to define the needs of the community with help of the existing EIBIR and ELMI/EAMNET networks, to consolidate the community into Euro-BioImaging nodes and associate centres and to demonstrate technical feasibility of the access and training concept for the different imaging technologies.
2. Construction. Nodes will be established and either newly constructed or established through major upgrades of existing facilities.
3. Operation. Euro-BioImaging nodes will provide access and training to users. Technology will be kept state of the art through continuous technology evaluation and development and through continuous upgrades of instrumentation at the nodes.

| Total preparatory cost | Total construction cost | Operation cost /year | Decommissioning cost |
|---|---|---|---|
| 10 Mio € | 20 Mio € per ALM node (4+1)<br>30 Mio € per MI node (4+1)<br>40 Mio € per common node (3)<br>370 Mio € total | 5 Mio € per year ALM node<br>15 Mio € per year MI node<br>20 Mio € per year combined node<br>160 Mio € per year total | |

***9. Timetable for construction, operation and decommissioning with duration and possible starting dates.***

| | | | |
|---|---|---|---|
| Preparatory phase<br>2 years | Construction<br>2-5 years (depending on sites and technology developments/upgrades) | Operation<br>15 years | Decommissioning |

| ***10. Reference: Person who has submitted the proposal, and will follow up in ESFRI*** | |
|---|---|
| Dr. Jan Ellenberg<br>European Molecular Biology Laboratory (EMBL)<br>Meyerhofstr. 1<br>D-69117 Heidelberg<br>Germany<br>T +49-6221-387-328<br>F +49-6221-387-98328<br>jan.ellenberg@embl.de | Prof. Gabriel P. Krestin, MD, PhD<br>Erasmus MC, University Medical Center Rotterdam<br>PO Box 2040<br>3000 CA Rotterdam<br>The Netherlands<br>T +31-10-7035987<br>F +31-10-7034033<br>g.p.krestin@erasmusmc.nl |

***1. Descriptive title, and information on the ESFRI delegation submitting the proposal (or one of the member of EIROForum)***

## European high security BSL4 laboratories building and networking

***2. Synthesis description of the new RI (or major upgrade) and S&T fields involved at Pan EU level in its use. Add links to relevant data/web pages***

In the context of emerging and re-emerging infectious diseases involving highly pathogenic micro-organisms there is a real need for Europe to be prepared to face such a threat. In case of pandemic outcome involving BSL4 classified pathogens, it will be of importance for the European countries to be able to manage diagnosis and the development of prophylactic and therapeutics means to fight these pathogens. Thus, it is needed to have enough BSL4 infrastructures at one's disposal. known BSL4 pathogens being present in developing countries, European BSL4 capacities have been poorly developed, even if recent effort have been made to face potential bioterrorist attacks.

In this context, there is a real need to create an adapted and coordinated Pan-European BSL4 task force in order to face any BSL4 classified pathogen related pandemic. Objectives of such a pan-European task force are: development of diagnosis, basic and finalised activities, biological resources management and training activities.

To reach these objectives, the project proposes to create a task force by conducting **four main actions**:

<u>To Build additional BSL4 areas on existing sites.</u>
The first one concerns the building of additional BSL4 area on the site of already existing BSL4 laboratories. The building of these new areas will permit to create and manage Biological Resource centre as recommended by OECD (www.**oecd.org**/document/36/0,3343,fr_2649_34537_3877720060_1_1_1_1,00.html), to separate diagnosis activities from basic research and R&D ones, to increase animal facility capacities. All existing European BSL4 laboratories will be involved in this action.

<u>To Build new BSL4 structures</u>.
Italy (National Institute for Infectious Diseases L. Spallanzani IRCCS Rome), Germany (Bernhard-Nocht-Institute for Tropical Medicine, Hamburg, Robert Koch-Institut, Berlin) and Netherland (National Institute for Public Health and the Environment (RIVM), Bilthoven) are planning to build new BSL4 laboratories and are involved in the project.

Spain has also expressed its interest in developing scientific activities related to BSL4 classified pathogens and the construction of a new BSL4 laboratory in this country will also be integrated in this project.

Since most of existing or planned BSL4 laboratories are located in western Europe (United Kingdom, Sweden, Germany, Italy and France), the building of two more BSL4 laboratories in eastern Europe (for example: Poland, Austria) will be examined.

<u>To Build support infrastructure.</u>
In order to help European countries that do not have BSL4 capacities to participate to the fight against BSL4 classified pathogens, it is of main importance to give access to such infrastructure to scientists from these countries. Moreover, at present time, most operators or on site users of BSL4 laboratories are mainly virologists belonging to the basic research community. However, it is clear that to solve health problems related to infectious diseases a multidisciplinary approach, involving for example academic immunologists and other community such as industry is needed and that more research teams need to have access to BSL4 facilities. Capacities to host scientific visitors in terms of experimental areas outside BSL4 laboratories and

offices are needed. The building of such infrastructures in existing or future BSL4 laboratories will be included in the proposal.

To create coordination capacities.
To avoid any redundant activities, to promote efficient collaborations and to facilitate exchange of information and experience, a specific body in charge of the coordination of all the activities at the European level will be created.

***3. Science case: scientific area(s) and potential and/or explicit users, how the new RI will fit into the existing and future landscape of Research and of existing RI's, at EU and World level.***

Health context:

Several emerging and re-emerging infectious diseases including viral haemorrhagic fevers such as Ebola, viral encephalitis like Nipah and others could have a major burden on socio-economic development in the developing countries and through migrations and global travels increasingly threaten the population of Europe as well. These micro-organisms highly pathogenic for humans are classified as biosafety level 4 (BSL4) pathogens and must be handled in high-security BSL4 laboratories.

Until now, only BSL3 pathogens such as SARS and avian flu epidemics have represented worldwide threats. But these emergences have demonstrated the reality of the infectious threat and our vulnerability in front of emerging or re-emerging infectious diseases. Moreover, the reality of the bioterrorist threat which includes the use of highly pathogenic micro organisms, such as BSL4 pathogens, must also be taken into account.

Finally, BSL4 classified pathogens are only, at the current time, represented by viruses and all BSL4 laboratories are designed and equipped for the handling of viruses. Yet, many experts do not exclude that within the near future other emerging micro-organisms such as multi-resistant bacteria (like *mycobacterium tuberculosis*) could be classified as BSL4 pathogens. This would lead to main modifications in the organisation and equipment of all the BSL4 laboratories.

Definition of the needs:

In this context, the scientific challenges are enormous and the survey and study of these agents are needed. The implementation of such strategy implies the development of diagnosis, basic and finalised research activities.

Diagnosis is essential for survey and characterization of the pathogen as well as for the constitution of a collection. Basic research is of great importance for definition of therapeutic and prophylactic targets and finalised research is necessary for the development of diagnostic, prophylactic and therapeutic tools. Specific training of all BSL4 users is also of importance to ensure maximum biosafety conditions. Finally, the constitution of BSL4 pathogens collection is essential for the achievement of all the activities cited below. All these activities are closely linked and to reach the needed high international level of excellence, each member must be able to cover all of them, in the highest quality manner.

At the present time, there are only 6 running BSL4 laboratories in Europe whereas the threat related to dangerous pathogens is increasing.

It is very difficult to define precisely the needs in terms of infrastructure. However we have learned from the recent avian flu and Chikungunya outbreaks. The first lesson has been that the disposal of diagnosis capacities was not sufficient to solve the problem. Indeed, after identification of these pathogens, it has been necessary to initiate research program to try to develop prophylactic and therapeutic means. Concerning the Chikungunya outbreak in "La Reunion",

more than 10 BSL3 laboratories, including animal facilities, have been activated, in France only. Even though the virus has only threatened the South part of Europe, BSL3 laboratories have been solicited all over Europe. In the case of H5N1 threat, whereas no human cases have been detected in Europe and no inter human contamination demonstrated; over 20 BSL3 laboratories had to work on the virus.

Moreover, capacities for testing new vaccine or new therapeutics tools on animal models remain insufficient since for example only one BSL4 laboratory in Europe (Lyon, France) has capacities to work on non human primate models.

Another issue has to be taken into account: each 12 or 18 month BSL4 facilities have to be closed for approximately 2 months for global maintenance, limiting then the capacity of activities.

Taking into account all these remarks, it seems clear that with only 6 running BSL4 laboratories Europe would not be able to face a real BSL4 classified pathogen pandemic situation. Thus, there is a crucial need to have more BSL4 spaces and also experts available. Most of the existing BSL4 laboratories host only research and diagnosis activities and lack biological resources management and training capacities. It thus implies building of additional BSL4 areas for implementation of all activities including increased hosting capacities. Moreover, BSL4 laboratories are located within western Europe and even if it is of interest to provide with such infrastructures one more western countrylike Spain, a broader distribution of these infrastructures involving one or two more BSL4 laboratories in eastern Europe would also be very efficient for fighting infectious diseases.

Potential users:

Most users or operators of existing BSL4 laboratories are virologists who belong to the basic research community. It seems of major importance to be in situation to develop adapted scientific programs that scientists belonging to other scientific specialties such as immunologists or chemists and to other community like industry can have access to BSL4 facilities. Of course **access** must be given, under specific security processes, **at the international** level.

Conclusion:

To conclude, it is virtually certain that as the creation of BSL3 facilities and networks for the study of HIV in the 80s led to major scientific discoveries, the increase in BSL4 laboratories capacities and the reinforcement of coordination efforts will have a major impact on our knowledge of high pathogen infectious mechanisms and on health progress.

The new research infrastructure, described in the proposal, will permit to address scientific urgent questions in term of diagnosis, prophylaxis, therapy and to face efficiently the emergency of new viruses.

## *4. Technical case: summary of results (technical specifications) of conceptual and/or technical design studies.*

The 4 main actions that are proposed to reach our objectives (to increase research, diagnosis, biological resources management and training capacities of the European BSL4 laboratory network) concern the building of new BSL4 area on existing BSL4 infrastructure sites, the building of new BSL4 laboratories, the building of support infrastructures and the creation of a European coordination body.

The conceptual design of a BSL4 laboratory:

Each BSL4 laboratory needs to be designed and scaled to host the four main activities needed to fight infectious diseases, diagnosis, microoganisms collection, research and training. All

these activities cannot be performed in the same area. Diagnosis activities must be separated from research to avoid any false diagnostic results that could be generated through sample contamination with concentrated viral preparation used for research activities. Moreover, since no efficient manufactured diagnostic tools are available for BSL4 pathogens, the diagnostic room must also be designed to integrate GLP (good laboratory practice) standards for the production of reagents. Since diagnostic activity will generate additional strains and because collection must also be protected from any contamination, the collection room must be closely linked to the diagnostic room. The research units must be designed to accommodate at the same time experiment involving different microorganisms. Because research units are used for research activities and also for training, it has also to be scaled and equipped with enough emergency exits to avoid limiting accesses. Animal facilities can be directly linked to research unit and must be scaled and designed to house all pertinent and permitted animal models.

Of course, activities involving BSL4 pathogen are very dangerous and sensitive, and each BSL4 laboratory holder has to define and set up specific security plans. Security is one of the expertises that will be shared and implemented between all BSL4 units. This implies to create a specific workpackage in charge of security aspects which will be shared with all new participants.

In each case international standards will constitute the references for conception of new BSL4 areas as well as for quality, biosafety and biosecurity management. international guidelines such as the WHO guideline for the safe transport of infectious pathogens (http://www.who.int/csr/resources/publications/WHO_CDS_CSR_LYO_2004_9/en/), the Laboratory Biosafety Manual Third Edition (http://www.who.int/csr/resources/publications/biosafety/WHO_CDS_CSR_LYO_2004_11/en/), the CDC biosafety guideline (http://www.cdc.gov/od/ohs/biosfty/biosfty.htm) or the recommendation guideline for Biological Resource Centre edited by OECD (http://www.oecd.org/document/36/0,3343,fr_2649_34537_3877720060_1_1_1_1,00.html) will be used in the conception, building and management of the new BSL4 infrastructure.

Building of additional BSL4 areas on existing sites:

For each existing laboratory an analysis of the capacities will be performed and compared to the needs before a proposal is established. For each, addition of diagnostic room, BRC room, research area and animal facility will be studied. National regulation will always be taken into account.

Building of new BSL4 structures:

Concerning the building of new BSL4 laboratories, the project will integrate all the new design and organization concepts gained from the past experience of current holders, including the integration of capacities for animal models development.

Buildings support infrastructure:

In each involved institute a specific study for building of support infrastructure will be performed. The study will take into account needs in term of space, but also specific needs to host multi-disciplinary research teams.

Creating coordination capacities.

This RI will of course need the implementation of centralized external governance that will have to coordinate the activities. The coordination in case of pandemic outbreak is of main importance since it will lead to an efficient dispatching and control of all activities required to face such situation. For this, a management structure including a steering committee and a scientific advisory board will be implemented. During the preparatory phase an additional and specific project team, including a dedicated project manager, will be created. Organisation of specific

workpackages in charge of management of experimentation, diagnosis, biosafety, security, ethic, legal and societal issues. Of course the coordination body will set up strong links with the ECDC for the management of BSL4 classified pathogens related outbreak.

It is of note that European coordinated networks concerning high-security facilities (EURONETP4, ENP4Lab, ETIDE, ENIVD) have now been created. ENP4Lab, that has replaced EURONETP4 (http://www.euronetp4.com/), is a European Union project sponsored by the DG-SANCO Public Health program that networks European BSL4 laboratories. It aims to enhance co-operation, communication and exchange of information between BSL4 laboratories in Europe with a specific focus on biosafety and biosecurity issues and diagnosis activities. Since that project gathered all existing and future BSL4 laboratories, it could constitute the frame of the coordination body.

Moreover, Biobanking and investigation of samples that may contain BSL4 pathogen is essential to study pathogen host interaction as a basis for new diagnostics and therapies. In this this way and collaboration with the Biobanking and Biomolecular Resources Research Infrastructure (BBMRI, http://www.bbmri.eu) a concept will be developed for biobanking of human biological samples containing high risk pathogens."

The distributed European infrastructure will not work with complementary BSL4 units but will take advantage of distributed competences and expertises in all the European space.

***5. e-infrastructure: what does the new RI require as far as e-infrastructure? How is it integrated with the existing EU e-infrastructure (e.g. Geant, grid, digital repositories).***

In the frame of a European P4 network constitution, sharing information and harmonizing processes are essential. In this view, three actions could be developed:

1. Harmonization of the internal information management processes, particularly in the fields of the quality assurance, the biosafety and biosecurity risk assessment;
2. Standardization of the identification and the description of the biological material in order to provide data through common description formats and standard exchange files (e.g. XML) for classified and free access catalogues;
3. Creation of an e-infrastructure, with different levels of security including highly secured level for BSL4 authorized staff only, which gives, among other data, the availability of diagnostic rooms and animal facilities of the network members, in case of emergency.

Of course, exchanging all information, especially those classified as sensitive or confidential, through e-infrastructure is difficult but possible to secure. However, all activities and related information conducted in BSL4 laboratories do not need highly secured exchange channels. Taking into account all these features, an efficient service oriented e-infrastructure for the BSL4 network can equip European Research Infrastructures with a unique virtual BSL4 facility.

Existing websites would be, of course, invited to join the network, e.g. Euronet P4 website (http://www.euronetp4.com/).

***6. Other expected socio-economic impacts: development of new technologies, effects on training, involvement of industries, local impact, other).***

The health sector is one of the main economic sector and large investments are made to fight diseases on a global scale. In this field, infectious diseases control is one of the main challenge which requires the development of new drugs, vaccines, and diagnostics tools.

As explained below, the main missions of such infrastructures can be divided into 4 categories, diagnosis, research, biological resources management and also training. Training of people

that will work in such laboratories is of great importance since each action to be done can have

major health consequences and must then be previously calculated and described in a specific procedure guide. Training of people implies also that time and space be available and managed. To reach such objectives broad and well organised BSL4 area must be available. It includes the separation of research activities from diagnosis and resource management ones.

Concerning involvement of industries, it is of note that, the close relationship that currently exists between some existing BSL4 structures in Europe and health industries has demonstrated its capacity to help industrial development as well as the crucial role it plays in the success of these developments. This acquired experience should be useful to reinforce and increase the collaborations between research and industrial actors of the domain. To facilitate and encourage such associations an increase in infrastructures and biological resources circulation capacities would be of first importance.

***7. Commitments / maturity: which States / Organizations have demonstrated interest / commitment in supporting and/or funding the proposal?***

Europe already has a history in the study of highly pathogenic micoorganisms as demonstrated by the existence of BSL4 laboratories in some European countries, by networking activities in that field and edition of guidelines as well as exchange or information for the management of biosecurity and biosafety issues.

Existing European Infrastructures:

There are 6 existing running BSL4 laboratories in Europe. The first ones were constructed in UK (Porton Down, http://www.hpa.org.uk/cepr/specialpathogens/default.htm) and Germany (Marburg and Hamburg). Within the 90s 3 other countries have built such facilities, France with the Inserm Jean Merieux P4 Laboratory in Lyon, Italy in Rome at the L. Spallanzani hospital and Sweden in Solna at the Swedish Institute for Infectious Disease Control. **All of them are supported by governmental funds.**

Future BSL4 laboratories already planned:

Moreover in front of emerging infectious diseases threat some European countries already planned to build new BSL4 laboratories within the coming years. In Italy, a large BSL4 infrastructure including clinical facilities to house and treat infected patients and a BSL4 laboratory is under construction at the L. Spallanzani IRCCS in Rome to replace the existing one. In Germany, a new BSL4 laboratory is under construction in Hamburg at the Bernhard-Nocht-Institute for Tropical Medicine to replace the small old one, and the building of a new one is planned in Berlin at the Robert Koch-Institut. **The building of all these new infrastructures are supported by governmental funds.**

Networking activities:

Since 9/11 and more recently with the SARS and avian flu emergencies European countries as other countries all over the world have realized that highly dangerous micro-organisms emergency can represent a serious threat.
Concerning BSL4 classified pathogens, this awareness has lead to the creation and funding in 2004 for 3 years of a BSL4 laboratory network entitled EURONETP4 (http://www.euronetp4.com/). This action has been renewed for 3 more years in 2007 through the funding of ENP4Lab. The main outcomes consisting in harmonization and standardization of practices within biosafety and biosecurity domains to ensure a better interoperability and comparison of results. The partners of the project are Italy (National Institute for Infectious Diseases L. Spallanzani IRCCS Rome), Germany (Bernhard-Nocht-Institute for Tropical Medicine, Hamburg, Philipps-Universitaet Marburg, Marburg), United Kingdom (Health Protection Agency, London), Sweden (Swedish Institute for Infectious Disease Control, Solna) and France (National Institute for Health and Medical Research, Lyon). Observers have also been inte-

grated in this project (Österreichische Agentur für Gesundheit und Ernährungssicherheit Spargelfeldstraße 191, Wien, Austria, Robert Koch-Institut, Berlin, Germany, National Institute for Public Health and the Environment (RIVM), Bilthoven, Netherland).

Within the recent past, other networking project (ETIDE; ENIVD) mainly focusing on the diagnosis of BSL4 classified pathogens were funded by EU. ETIDE (http://www.etide.eu/default.aspx) project funded by the DG Health and Consumer Protection since 2006 for a 3 years period aim to produce a training program and training materials specifically to enhance **European** capacity to recognize and respond effectively and in a coordinated fashion to infectious disease emergencies. The ENIVD project (http://www.enivd.de/index.htm) funded by the DG SANCO aim to exchange and gather information that can improve the diagnostics of "imported" viral diseases in Europe. Members of the ENP4Lab network participate to these 2 EU projects.

Guidelines for biosafety and biosecurity issues:

Since activities involving BSL4 pathogen are very dangerous and sensitive, each BSL4 laboratory holder has been obliged to define and set up specific security plans. All these plans have been based on recommendations included in international guidelines such as the WHO guideline for the safe transport of infectious pathogens (http://www.who.int/csr/resources/publications/WHO_CDS_CSR_LYO_2004_9/en/), the Laboratory Biosafety Manual - Third Edition.

(http://www.who.int/csr/resources/publications/biosafety/WHO_CDS_CSR_LYO_2004_11/en/), the CDC biosafety guideline (http://www.cdc.gov/od/ohs/biosfty/biosfty.htm) or the recommendation guideline for Biological Resource Centre edited by OECD (http://www.oecd.org/document/36/0,3343,fr_2649_34537_3877720060_1_1_1_1,00.html).

Of course security expertises have been gained by the past by all BSL4 laboratory holders and will be shared by all future BSL4 units.

Organization that have demonstrated interest in supporting the proposal:

All institutes holding BSL4 laboratories are concerned by this project and have been contacted. Most of them, like the National Institute for Public Health and the Environment (RIVM) in Bilthoven, the Health Protection Agency in London (United Kingdom), the Swedish Institute for Infectious Disease Control in Solna (Sweden), the “Österreichische Agentur für Gesundheit und Ernährungssicherheit Spargelfeldstraße” in Vienna (Austria) and the National Institute for Health and Medical Research in Lyon (France) have expressed their interest in this proposal. Some others that have already build or are building new BSL4 laboratories like the Bernhard-Nocht-Institute for Tropical Medicine in Hamburg (Germany) or the National Institute for Infectious Diseases L. Spallanzani IRCCS in Rome (Italy) are mainly interested in the networking activities included in the proposal.

Spain, as a non BSL4 laboratory, has expressed a great interest in the proposal. Of course, all other EU countries will be officially contacted during the preparatory phase through their research and health ministries.
Three European countries, Italy, Germany and the Netherland have already committed funds to build new BSL4. All the countries that have or plan to have BSL4 laboratories have committed to ensure operation cost of their national infrastructure.

***8. Costs for construction, operation and decommissioning, indications on project financing. Give budget info in Mio €***

Preparatory cost:
For the 3 years of preparatory phase a team of 3 permanent people including a senior scientist as project manager, an engineer and a secretary will be constituted. Consultation of architects

and consultants firms will also be needed. The estimated cost of this phase is 5 Mio €.

Construction cost:
The estimated surface area that will be added to existing BSL4 laboratories is 100-200 $m^2$. The one for new BSL4 laboratories including all activity capacities is 350 $m^2$. Based on our recent experience, the construction cost of a 100-200 $m^2$ BSL4 facility is 10 Mio € and the one of a 350 $m^2$ BSL4 facility is estimated at 15 Mio €. Thus, for the construction of additional BSL4 areas to existing BSL4 laboratories the cost will represent 60 Mio € (6x10 Mio €), for the construction of new BSL4 laboratories the cost will reach 90 Mio € (6x15 Mio €).

The estimated construction cost of support infrastructures to existing and future BSL4 laboratories is 24 Mio € (12x2 Mio €).

Operation cost:
The operation cost of the French 200 m2 BSL4 laboratory, excluding experimentation cost, is 2 Mio €/year. The total operation cost for 12 European BSL4 laboratories will thus be 24 Mio €/year.

| Total preparatory cost | Total construction cost | Operation cost /year | Decommissioning cost |
|---|---|---|---|
| (of which already spent or committed)<br><br>5 Mio € | (specify contributions committed or indicated by possible funders)<br><br>174 Mio € (50% from national funds) | (specify contributions by possible funders)<br><br>24 Mio € (60% from national funds and 20% from private funds) | (possible funders) |

***9. Timetable for construction, operation and decommissioning with duration and possible starting dates.***

Preparatory phase:

During the preparatory phase, a detailed evaluation of needs for each existing and future BSL4 infrastructures will be performed. It will be followed by a design study phase of new BSL4 areas including financial aspect. At the same time the coordination body, including centralized small groups for coordination, will be defined and implemented. Finally, consultation of stakeholders will be performed. The duration of this phase, based on our experience gained during the building of existing BSL4 is estimated to be 3 years.

Construction phase:

The construction phase will include the building of new BSL4 areas and support infrastructures but also the validation of all new area and laboratories. The operational validation of BSL4 laboratories, that include technical validation of the infrastructure but also implementation of all procedures, is a very important and obliged step before obtaining all authorization to operate the infrastructure. It can represent the longest step of the construction phase. As an example, the French BSL4 laboratory in Lyon has been built in one year but the authorization to operate has been obtained over 2 years later. The estimated duration for the construction phase in this project is 5 years.

Operation phase:

Since BSL4 laboratories are regularly maintained and upgraded when needed, there is no rea-

| | | | |
|---|---|---|---|
| son to limit the operation phase. | | | |
| Preparatory phase<br>36 months | Construction and validation phase<br>60 months | Operation | Decommissioning |

***10. Reference: Person who has submitted the proposal, and will follow up in ESFRI***

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***1. Descriptive title, and information on the ESFRI delegation submitting the proposal (or one of the member of EIROForum)***

**European Marine Biological Resource Centre (EMBRC)**. A consortium of the main coastal marine laboratories in Europe with a capacity for access to models genomics, acting as a distributed infrastructure for high-level research in basic biology, marine biology and ecology including integration with modern technology and 'omics' platforms. Providing and promoting access to the infrastructure for marine biological researchers, for training the researchers of tomorrow as well as a resource for SMEs and industry. Generating and leading outreach to stakeholders (both the public and industry).

***2. Synthesis description of the new RI (or major upgrade) and S&T fields involved at Pan EU level in its use. Add links to relevant data/web pages***

This proposal seeks to establish a European Marine Biological Resource Centre (**EMBRC**) designed to support the needs of the ERA in basic biology, marine biology and ecology and to foster its integration with other fields of sciences, including genomics and systems biology for the next 30 years. This infrastructure will also act as an incubator and 'spin-off' for new ideas and technologies and will work with and alongside academics, SMEs and Industry to apply these at the European level. Marine organisms are an essential component for our quality of life, for their contribution to the food chain and impact on the environment. However, given the difficulties in maintaining and culturing them they are the least well studied.

Marine models have provided experimental systems for seminal discoveries in basic science that impact on our quality of life in a concrete and lasting way (cf. Nobel prizes for Physiology or medicine 2001, 2000, 1970, 1963). Thus, it is highly likely that marine organisms with their phylogenetic diversity offer access to presently unknown biological mechanisms which can in turn be used for biomedicine or for biotechnologies. **EMBRC** will be a distributed infrastructure comprising key coastal marine laboratories with complementary expertise and equipment providing i) access to marine laboratories, which encompass a representative set of European coastal ecosystems, fully equipped with modern boats, sampling devices and platforms in sequencing, transcriptomics, proteomics, metabolomics, structural biology and bioinformatics; ii) an integrated supply of key marine microbial, algal or animal organisms, as existing and new models for interdisciplinary marine biological research; iii) services from a central DNA and cell stock centre for marine model organisms, backed by dedicated platforms for the preparation of DNA libraries, cell lines and specific genotypes for functional genomics, including transgenic and mutant lines.

This infrastructure will build on and expand on the synergies developed in FP6 between the partners (See ***Marine Genomics Europe*** and ***MarBEF*** links below) and current activities in FP7 where we are active in the current call for I3 (***ASSEMBLE***).

**Access.** Facilities are all currently accessible through mutual agreement and common projects (national or European). The infrastructure will provide seamless access to all sites and facilities for end-users.

**Potential users. Marine Biologists** working on a wide range of interests from resource management, biodiversity, trophic structure to biotechnology and conservation biology. **Government and NGO Environmental Agencies**. **SMEs** with interest in biotechnology. **Researchers** using molecular biological and genomic approaches, in biomedicine, biochemistry, physiology, systematics, paleontology, ecology and research on global change and climate. **Companies** in aquaculture and those developing new materials, e.g medicines and bio-fuels.

### *3. Science case: scientific area(s) and potential and/or explicit users, how the new RI will fit into the existing and future landscape of Research and of existing RI's, at EU and World level.*

Europe has a distinguished history in Marine Biology with its marine biological stations established in the late 19 th Century. They represented and represent a major European infrastructure that has acted to serve, enhance and develop collaborative marine research worldwide. Now, however, they have become a new breed of marine research stations, developing and applying new technologies and facilities that allow a higher quality of service, not only to the marine biological community but also to the increasing numbers of scientists that are turning to marine organisms as models with which to investigate fundamental questions in biology.

By providing access to fully equipped research laboratories next to coastal ecosystems, supplying access to living organisms and by carrying out their own in-house research programmes, marine research stations already act as research infrastructures for transnational access and, altogether, they represent a major asset for the European science community. Recent years have seen an increased interest in marine model organisms because of the emergence of cheap, rapid genome sequencing. The aim of integrating them will then be to capitalize on the complementarity and potential interoperability between marine institutes. The activity will primarily directed at 'de-fragmenting' this set of infrastructures, by providing increased opportunities for research, access, collaboration and training. The outcome will be the creation of a major European distributed research infrastructure. In addition, the point must be made that in many instances, facilities and technologies need to be continuously improved. Among the vast body of necessary technological improvements, a number of joint research activities will be selected with the aim of maximizing technological collaboration between sites. These actions will fall into three main categories: i) Improvement of instrumentation for access to the biodiversity of coastal ecosystems ii) Improvement of the production, maintenance, provision and utilization of key marine models for biological sciences and iii) The functional analysis of ecological or biological models, using modern, systems biology approaches.

Transfer, expansion, improvement of quality and quantity of the newly developed technologies will involve a combination of workshops, practical courses and research with shared personnel**.** At the same time the links between SMEs, Industry and research institutes will be addressed in **imaginative outreach programs**. Physical restructuring will allow industrial and institutional partners to work alongside each other in new ways to provide new products outputs and solutions.

At the global scale this Infrastructure would provide one of the largest integrated marine biology platforms in the world, providing European scientists with cutting edge tools to address global issues. For a case pointing towards the creation of a European long-lasting, multi-site institute see the Scientific Challenges document (a position document on basic European Research in integrated Marine Biology supported by **MarBEF**, **Eur-oceans**, and **Marine Genomics Europe**).

### *4. Technical case: summary of results (technical specifications) of conceptual and/or technical design studies*

Additional facilities are needed to integrate, marine biology and ecology with all areas of basic biological research. All the partners are arranged in a distributed infrastructure located by the sea and are equipped with model organism collection and maintenance facilities. The participants share state-of-art genomic and proteomic facilities.
- **Stazione Zoologica 'Anton Dohrn', Naples, Italy** Sanger sequencing (medium throughput), robotic picking, spotting and analysis of microarray, Real time PCR. Typhoon imaging.
- **Sven Loven Centre for Marine Sciences** (previously KMRS and Tjarno) Sweden. Real time PCR, Proteomics (medium scale), Culture collections.

- **Scottish association for Marine Science, Oban, UK.** Algal culture collections.
- **Station Biologique de Roscoff, (France).** Algal culture collections, Sanger sequencing (medium throughput), robotic picking, macroarraying, HPLC-MS, GC-MS microarrary/macroarray reading, , protein expression and crystallization, bioinformatics.
-**Observatoire Océanologique Banyuls sur mer (France).** Flow cytometry, imaging and platform for mass production of microorganisms. Access to 'omics' through Roscoff
-**Observatoire Océanologique Villefrance sur mer (France**). Advanced Microscopy and imaging, Sanger sequencing. Access to 'omics' through Roscoff.
-**CCMAR Faro Portugal.** Fish cell lines, Sanger sequencing, Typhoon imaging, HPLC-MS, GC-MS.
**-Plymouth Marine Partnership** (UK) led by The Marine Biological Association, (Plymouth Marine Laboratory, Sir Alistair Hardy Foundation for Ocean Science, and Plymouth University. Sanger sequencing and imaging.

The proposal is not designed to be exclusive especially partners from the Baltic Sea States and the Eastern Mediterranean are welcome. We will be seeking partnership with Alfred Wegener Institute for Polar and Marine Research Bremerhaven Germany.

**Additional technical infrastructure.**
1) **Upgrade** the capacity for holding, rearing and transporting marine model organisms, 2) **promote** the identification and establishment of new model organisms that are key players in ecosystems 3) **potentiate** the capacity to analyze genomes and gene expression profiles dedicated to marine organisms. 4) **disseminate** know how and accessibility for these organisms and enable ecologists and basic biologists to work on them 5) **build** (where appropriate) modern adjacent laboratories and 6) **generate** new integrative departments. 7) **foster** transfer of knowledge between EMBRC and industry, including the development of science parks next to the basic research facilities.

***5. e-infrastructure: what does the new RI require as far as e-infrastructure? How is it integrated with the existing EU e-infrastructure (e.g. Geant, grid, digital repositories).***

This will be both a physical and virtual (e) infrastructure. It will involve the development and physical expansion of the capacities of the marine institutes (this will be achieved by national, EU and industrial funding) to house and carry out research. This infrastructure will complement but not overlap with *LIFEWATCH* and ELIXIR (e-science and technology infrastructures for biodiversity data, observatories and data depositories) already on the ESFRI RM and with which we will be seeking partnership. EMBRC ***will not*** emphasise the compilation and production of long-term data series and complex biodiversity data, instead it will seek to carry out strategic and basic high level research which will underpin the EU knowledge base with the specific directive of addressing issues of improved quality of life and production. The data generated will feed into infrastructures (such as LIFEWATCH, ELIXIR and EBI (European Bioinformatics Institute), to unite the relevant systems biology information. However the main point to stress is that the objectives and outcomes of this distributed infrastructure will be essentially *practical* and *productive* with a strong emphasis on research, training and industrial partnership. In this sense EMBRC should be seen as complementary and completely compatible with other ESFRI Research Infrastructures.

***6. Other expected socio-economic impacts: development of new technologies, effects on training, involvement of industries, local impact, other.***

From the point of view of socio-economic benefits, marine organisms are of enormous interest, for two major reasons. First, the sea provides amazing biological diversity (of 34 fundamental phyla, 17 occur on land, whereas 32 occur in the sea and 13 are exclusively marine). The diversity of marine species, together with the relatively large number of species that are exclusively marine, are the reasons why the sea is an important new source of biotechnology

materials, chemicals and processes. Second, marine organisms often possess unique structures, metabolic pathways, reproductive systems, and sensory and defence mechanisms because they have adapted to extreme environments ranging from the cold polar seas at -2° C to the great pressures of the ocean floor.

Many marine products are currently commercialized or in development (see http://www.marine-genomics-europe.org/index2.php?rub=a&pid=23). Many more are in development, and more importantly many more are waiting to be discovered. A concerted action with production in mind would have an enormous social impact. At the local level an increased synergism between academia and industry should lead to greater opportunities for employment and productivity. Many of the regions where marine laboratories are located are in areas of medium to high unemployment. More than this, the exploitation of marine organisms for food and industrial processes, has an impact on one of the other main uses we make of the marine environment – ***leisure and recreation***. Scaling up these processes will have a direct and tangible impact on marine ecosystems and will certainly change the way we perceive this environment. One major objective of this infrastructure will be to develop a dialogue with industry and stakeholders through research to arrive at a common consensus on how to use, ***and not to abuse***, this resource.

**Training and recruitment**
We are presently recruiting people for environmental genomics, metagenomics and bioinformatics. We plan to continue recruiting more people in these areas. We need to train and recruit the Marine Biologists of the future, integrating training in organismal biology, ecology and omic sciences. This needs long term planning and integration. This will be achieved by concerted recruitment in the key 'omic' areas, targeted PhD programmes and workshops. This is highly realistic, for example the partner SZN Naples runs an integrated PhD programme which trains Marine biologists in both ecology and basic biology. This type of research school would become pan-european and targeted towards these high-throughput sciences. In particular, an international PhD programme in "Marine systems biology and biodiversity", currently involving 3 partners of EMBRC, is in preparation.

## *7. Commitments / maturity: which States / Organizations have demonstrated interest / commitment in supporting and/or funding the proposal?*

This proposal builds on the already highly developed synergy between the partners of FP6 networks of excellence, Marine Genomics Europe and MarBEF. Of the current partners in EMBRC (listed in section four), all the institutes have been and are currently working on joint network proposals, have a strong history of working together and have indicated possible funding interest though national schemes. At a recent meeting of the partners, it was estimated that, collectively, around 50 Mio € from national funds is planned for capital investment (mostly building labs and facilitates) within the next 5 years.

**Fitting the planned RI into existing facilities**
The current infrastructure, through the process of convergence created by activities in current FP6 and proposals for FP7, is already carrying out collaborative research in the area aimed at by the requested RI. However, we require upgrading of facilities (e.g., the ever decreasing cost of sequencing requires major investment in new technology), and we need to increase the functional capacity of the infrastructure. This process in itself opens up higher through-put and greater volumes of data which will need to be handled by computational biology techniques. No completely new facility is planned but the construction of new laboratories and of installations adjoining existing sites is envisaged.

**A history of sharing and cooperation that will be augmented by the RI**
There is a tradition of sharing facilities and access in marine laboratories which has been explicit since their inauguration in the 1880s'. Traditionally also, oceanographers have been used to close cooperation and collaboration because of the sheer size of their projects. Until recently, however, the community of marine biologists had remained very fragmented. Now we

are seeing a reawakening of this spirit of cooperation with the advent of the 'omic' sciences, which require equipment and analyses that are beyond the reach of single teams or even institutes. For the preceding reasons, this and earlier initiatives have been e recognized by the partners as being timely. There is enormous scope for improving cooperation, particularly between biomedical scientists, biological marine biologists and ecologists. This is where we feel the new frontier in Marine Science is, and this is here the major impact of this infrastructure would be.

**Summary of Objectives**
It would seem that the application of genomics and systems biology to biomedical Sciences, marine biology, and ecology will create the long awaited 'marriage' between large scale global considerations and biological systems (environment and human impact on it and human health and sustainable exploitation). Marine model organisms have a historical and future role in basic cutting edge biological research and in the future models should be selected which will also be representative of the wealth of traditional marine organisms used in ecological research. We see this dynamic as the front where the main future development of marine biology should be. This process needs resource channeling by close but foresighted management. We do not see this process as exclusive, though we do not see it fostering non cutting edge research either (such research would be positively transformed in this infrastructure).

***8. Costs for construction, operation and decommissioning, indications on project financing. Give budget info in Mio €***

The key European marine laboratories involved are probably collectively worth more than 1000 Mio € in patrimonial value, and they are spending a total on annual operating costs of ca. 30 Mio €. With perspectives for higher and sustained funding, EMBRC will seek to markedly upgrade and improve the level of access to research facilities, and provide and coordinate the supply of marine models and improve transnational access to coastal ecosystems. It will thus boost the efficiency of this unique infrastructure and further integrate the community of marine biologists. The costs indicated below are to be considered real costs for an effective upgrade.

| Total preparatory cost | Total construction cost | Operation cost /year | Decommissioning cost |
|---|---|---|---|
| € 10 Mio €, | € 100 Mio € | € 60 Mio € | |

***9. Timetable for construction, operation and decommissioning with duration and possible starting dates.***

**Preparatory phase.** Setting up management and governing board, identification of needs, strategic areas, concerted actions for the major capital initiatives required. Proposal construction, consultation with stakeholders. We expect consultancy and planning of the Infrastructure to take three years. To set up and run the EMBRC infrastructure would cost 7-10 Mio €. The EMBRC Infrastructure would be managed by a governing board including the SZN and all other partners. A dedicated management team with an e-interface for the exchange and acquisition of data and information will be built to provide a unique access point for the distributed infrastructure. The interface will include inventories of available services, and the modality of use of the infrastructure.

**Construction.** The construction phase will last 5 years and will involve the major costs of upgrading parts of the physical infrastructure, and the purchase of new equipment. Using as an example the current IPs and NoEs, we calculate that 20 Mio € a year would be needed for 5 years from National/local and EU funds and equivalent from national and regional funds.

**Operation.** Full implementation of the infrastructure for ten year operation period. Beginning during the construction phase and tailing off during the decommissioning phase. Operation costs are estimated as a fraction of current operating costs (ca. 30 Mio €/year). Hence if the national contributions to the operation of this Infrastructure is currently 30 Mio €/year then a step-up in the activity level would require an additional turnover of 30 Mio € (15 Mio € supplied by EU sources and 15 by national funding). This would lead to an operating cost of 60 Mio € /year for the time course of the operation phase.

**Decommissioning.** It is envisaged that once the infrastructure has been demonstrated to be functional and productive, its long -term function will be maintained by national funding and industrial sponsorship, with a relatively small input from the EU. European marine stations have grown and have been maintained for almost 140 years, in this new phase they will transform into a major European infrastructure with long-term prospects and thus in the future we would not expect there to be any major decommissioning costs.

| Preparatory phase 2008-10 | Construction phase 2010-15 | Operation 2013-33 | Decommissioning 2020-2040 |
|---|---|---|---|

***10. Reference: Person who has submitted the proposal, and will follow up in ESFRI***

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### 4.3.2 Emerging Proposals

***1. Descriptive title, and information on the ESFRI delegation submitting the proposal (or one of the member of EIROForum)***

**European Integrated Systems Biology Infrastructure (EISBI)**

***2. Synthesis description of the new RI (or major upgrade) and S&T fields involved at Pan EU level in its use. Add links to relevant data/web pages***

Systems Biology (SB) is at the current frontier of the Life Sciences (basic and applied) - dealing with fundamental Biology, Medicine and Biological Engineering. It represents a highly interdisciplinary approach to the understanding and harnessing of biological complexity. SB builds upon the great advances triggered by the "omics" revolution. It goes beyond them by combining high through-put experimental approaches in molecular biology, biochemistry and chemistry with bioinformatics, novel physics and engineering technologies, together with sophisticated mathematical approaches, (including modelling and simulation). Consequently, SB does not sit comfortably in any single department or even a classical university faculty. It demands new intellectual and organisational structures to deliver its full potential. It is not accidental that SB took off with the founding by Leroy Hood, Rudi Aebersold and Alan Aderem of an independent Institute of Systems Biology in Seattle - which combined technology development, experimental biology and mathematical modelling.

Systems Biology has become a viable approach as a result of recent developments in the biological and medical sciences, systems engineering, imaging, mathematics and computing. It uses an iterative cycle of computational modelling and laboratory experiments to study how the components work together in an integrated system, a characteristic feature of SB. This approach offers a wealth of opportunities to understand and utilise biological complexity rather than deconstruct it in a reductionist mode. Along with Synthetic Biology, it is very important to the future of the European economy, e.g. in the pharmaceutical and biotechnology industries. Currently, the US leads the world in many aspects of SB. There is, therefore, an urgent need in Europe to establish new organisational structures that facilitate the sharing of knowledge and expertise, the exchange of data and models, and the creation of new educational programmes to train Systems Biologists. This is the proposed role of EISBI, a distributed infrastructure aimed at providing coherence, critical mass and focus within Europe, to promote best practice, standardisation and joint working - maximise return on investment and enable the realisation of large-scale integrated research programmes.

***3. Science case: scientific area(s) and potential and/or explicit users, how the new RI will fit into the existing and future landscape of Research and of existing RI's, at EU and World level***

It is envisaged that EISBI will comprise a single distributed entity, formed from a number of well qualified SB institutes that have been established, or are in the process of being established, in Member States. The aim is to create an infrastructure in which the sum is significantly greater than the individual parts. The new infrastructure will be much more than simply a network of SB institutes. Each Institute will contribute a group of internationally recognised researchers ranging from biologists, biotechnologists and medics, to mathematicians and engineers, to computer scientists and physicists. Each Institute will bring to the EISBI significant experimental and mathematical analysis capabilities and infrastructure, comprising well found laboratories, research staff, information systems and, in many cases, teaching programmes. Model organisms (uni- or multi-cellular), and model cell populations (e.g. immune cells, skin cells, liver etc) are currently providing fruitful approaches for Systems Biology research, using both discovery-based and hypothesis-based strategies. New directions in SB research are providing opportu-

nities to study interactions of organ systems and even populations in plants and animals, thus promising new advances in medicine, ecological management, the food industry and animal husbandry. The underlying concept is that EISBI as a whole will cover a broad biological spectrum consisting of systems, populations, organisms, organs, tissue, cells, proteins and genes (the Biological Continuum or BC). The infrastructure which underlies this comprises an advanced information system described in Section 4 of this document associated with a structured system to promote the identification and structured delivery of joint goals.

Since progress in life-sciences research depends upon the continued development and use of high throughput and other technologies supporting fundamental research activities, individual Institutes or combinations of Institutes will make use of the proposed EISBI infrastructure, within the limit of capacity, to provide the following services to the European Scientific community:

(i) Technology and Data Generation: Microarrays, DNA sequencing, mass spectrometry and imaging (these were instrumental in the rise of Systems Biology). Continuous technology development will increase throughput and efficiency, improve accuracy and sensitivity, and decrease the cost of the work. High throughput sample analysis methods for biological (encoded) molecules and of the substrates and products of cellular and organ metabolism are in a phase of rapid development. This is a natural interface with the growing science of nanotechnology.

(ii) Data Management: Modern data generation techniques generate enormous datasets. The Collection, processing, annotation and integration of experimental data will be a challenge for EISBI. Development of adequate data handling and transfer methods will stimulate interaction with the ICT industry.

(iii) Collaboration with: EBI, ELIXIR, Swiss Institute of Bioinformatics and similar organisations or infrastructures is envisaged (see also section 5)

(iv) Data Visualisation and Analysis: Bioinformatics tools and modelling software will be provided to simulate the dynamics of biological processes or systems, and to compare simulations and experimental observations - with the aim of validating research hypotheses. This is also an area with significant potential for future development.

(v) Translation of Knowledge: Examples are the translation of technological innovation into biotechnology products; the translation of medical innovation into clinical applications; and the translation of ecological/animal knowledge into sustainable changes of environment and food production.

Integration of selected research institutes in the EISBI research infrastructure will be predicated on their formal commitment to and performance of a number of tasks:

- Coordination of research activities and technology developments with colleagues, and promotion of collaborative approaches across Europe
- Strong support and commitment on the part of the National Governments, Agencies and international facilities
- Participation in appropriate collaborations by mutual agreement with staff in other EISBI institutes, other research institutes and Universities.
- Integrating into the Institute existing expertise and infrastructures for the translation of knowledge and innovation (e.g. medical and clinical centres, biotech, etc).
- Sharing the infrastructures and technology platforms of the constituent Institutes with selected, qualified visiting scientists, within the limit of capacity reserved for this purpose. In all cases, prioritisation of access will be performed by the assessment of project quality, e.g. as done for access to synchrotron and other structural biology facilities by EMBL.

- Contribution to the education of the next generation of Systems Biologists, by training qualified students from other institutions in special courses and workshops and in the context of shared research projects, within the limit of capacity.
- Agreeing to open access for data, tools, algorithms and programmes on publication

In many ways the EISBI is expected to play a compound role in promoting Systems Biology in Europe, similar to that played by EMBL in promoting Molecular, Cellular and Structural Biology and Bioinformatics. The EMBL is a world-class centre that combines research infrastructures, pioneering research projects and advanced training - operating in 5 European locations (Heidelberg, Hinxton, Grenoble, Hamburg and Monterotondo). It has also established nationally funded partnerships with suitable institutions in Member States. The participation of the EMBL will help the EISBI become an integrated (albeit distributed) Research Infrastructure - with a major impact on promotion of Systems Biology in Europe.

An important role of the EISBI will be the identification, structuring and support of very large–scale research programmes which are currently beyond the capability of single European institutions (examples might be in the systems understanding of multi-factorial diseases, bioenergy and bio-manufacturing etc). Efforts to assemble these on an individual basis as stand alone projects involve an enormous overhead of duplicative effort in establishing the information and management infrastructures necessary to sustain them.

### *4. Technical case: summary of results (technical specifications) of conceptual and/or technical design studies.*

An important aim of the EISBI is to provide an information infrastructure, which is, for example, capable of supporting imaging and modelling from the systems level to the gene level. This will involve integrating a range of existing imaging modalities and models, as well as incorporating new techniques which will be/are being developed within the proposed member institutes of the EISBI and beyond. As other imagining modalities and better image processing techniques become available, they will be incorporated. The objective will be for the EISBI to be equipped with the best instrumentation to address research problems across the BC. It is, therefore, envisaged that the constituent institutes will be connected via a high-speed network (web-based as far as possible) to enable access to a wide range of facilities.

In a number of cases, the participating institutions also have a strong engineering/physical science base which is participating in SB research. Again, it is envisaged that as new instruments and methodology (eg imaging and visualisation) are developed, they will be incorporated into the work of the EISBI. Conversely, where the biological research requires new instrumentation and methodology to be developed, this will also be addressed. One of the key reasons for establishing the EISBI is to leverage existing facilities and expertise. Consequently, individual participating institutions will represent foci of expertise. The aim will be to integrate such foci in order to develop an infrastructure which can be accessed by all the partners. This will provide an important framework for research collaboration.

The plan is to link the EISBI with a number of existing infrastructures, including INSTRUCT (Integrated Structural Biology Infrastructure for Europe), ELIXIR (European Life Sciences Infrastructure for Biological Information), EATRIS (Network of Distributed Infrastructures for Clinical Trials) and ECRIN (European Advanced Translational Research Infrastructure in Medicine). The EISBI will also be linked to other engineering/physics based infrastructures that have carried out detailed work in relevant areas of biomedicine (eg SIMILAR). The facility will also draw, in its establishment, on the extensive networking which already exists between centres as a result of projects funded by e.g. the EC and ERASysBio/SysMo, and the extensive work done by the EC in FP 5&6 in underpinning areas such as standardisation and model development. It will also work closely with the ERA Instruments Programme on biological research instrumentation in Europe.
EMBL (and the other European Intergovernmental Research Organisations – EIRO's) have the

advantage of a centrally provided and managed budget; whereas, the EISBI will primarily depend on national funding for each of its component institutes, complemented by competitive European funding. To avoid wasteful duplication of efforts and to ensure that individual institutes are adequately funded and performing well, the EISBI will have a strong Management Board and Director, subject to supervision by an International Scientific Advisory Board and Financial Committee. The participation of individual Institutes will be reviewed periodically and will depend on assessed performance, in terms of science, technology, training, collaboration and financial sustainability.

***5. e-infrastructure: what does the new RI require as far as e-infrastructure? How is it integrated with the existing EU e-infrastructure (e.g. Geant, grid, digital repositories).***

The information challenge in systems biology stems from the need to capture, archive, maintain, distribute and achieve interoperability and integration of many different types of data from many different sources, and to provide the associated tools and models for its analysis, for teams and programmes with a very wide range of different skills and interests. The vision of the EISBI is to create a European SB infrastructure (rather than simply a Network) which supports and integrates this diversity. As described a previous section, this requires the establishment of an infrastructure of facilities (eg scanners, microscopes etc) which are available to all of the participants in the EISBI. In addition, modelling will be an important aspect of the research. There are now XML-based languages (eg CellML) which allow the sharing of models. For the vision of the EISBI to work, it will be necessary to establish an information infrastructure, ie an e-infrastructure which is principally web-based. The aim is for the EISBI to use, where possible and appropriate, existing European e-infrastructures, such as GRID and GEANT (although additional facilities may be available, eg the image database created by the SIMILAR Network of Excellence).

A significant number of the participating institutions have engineering departments with major expertise in e-infrastructures. The objective will be to create an EISBI e-infrastructure which builds upon what already exists - but is based on a strategy of using standard hardware, standard operating systems and is, as far as possible, web-based. For example, much of the high throughput technology that will be used generates large amounts of data; however, this situation occurs in a number of fields and standard technology is available which effectively addresses such problems. Another example is biomedical image database which has been established as part of the SIMILAR Network of Excellence. This is routinely accessed by about 30 institutions throughout Europe. Such facilities allow the development of advanced, often automatic, processing and analysis techniques – as well as effective joint *in vitro/in silico* research strategies. There is a growing SME community associated with this field which would be fully engaged (e.g. www.visbion.com)

***6. Other expected socio-economic impacts: development of new technologies, effects on training, involvement of industries, local impact, others.***

The impact of SB will be profound and ubiquitous. Systems biological approaches will enable understanding at the molecular and genetic level to be related to the functioning of complex biological systems in a predictive manner. This will give a greatly improved ability to make interventions to change or correct the behaviour of living systems and to design and introduce new functionalities into them. Consequently, SB promises economic and social benefits in almost every aspect of life. Ultimately it may enable the “laws” governing the design and behaviour of biological systems to be described (as they have been for physical and chemical systems).

In biomedicine, systems approaches offer the prospect of a serious step up in our ability to prevent and treat complex multi-factorial disease – including the major problems of ageing (e.g. diabetes, heart disease, stroke, arthritis…). In doing so it promises a revolution in the pharma-

ceutical industry, accelerating the move towards so-called “personalised medicine” in which interventions are much more closely structured to the individual, and which will greatly reduce the problems caused by the side effects of current drug treatments. These developments will fuel a growth in companies associated with systems-based knowledge and tools, alongside the pharmaceutical industry. Greater understanding of host-pathogen interactions – in humans and farm animals – will inform the management and treatment of infectious disease, which is becoming a serious issue globally but is of particular concern in developing countries.

Systems biology in plants offers the prospect of developing new approaches to disease and pest resistance, yield improvement and environmental impact reduction in crops. Much of this will come from better understanding of the rhizosphere – the complex system of interactions between the roots and the soil - and the use of predictive approaches to target interventions for specific crops at the farm level.

However, the most significant non-medical impact of systems biology in the medium term is likely to be in energy and biotechnology. It will enable us to more rapidly harness the power of bacterial or plant systems to make things, especially energy sources and manufacturing feedstocks (but also e.g. pharmaceuticals). There are environmental benefits in terms of reduced use of petrochemicals but also economic and social benefits in terms of increased economic return from the agricultural sector and the associated development of rurally-based processing industries. The economic contribution of biotechnology will be greatly boosted by “synthetic biology” – the engineering of improved or novel production functions in microbes, building on the knowledge of metabolism and synthesis pathways gained from major systems biology programmes.

Associated with the systems biology revolution will be a healthy growth in the industries supporting specialist tools and technologies underpinning the necessary R&D: particularly, analytical software and high-throughput instrumentation.

The applications of systems biology present some serious challenges for society, particularly in aspects of healthcare and when coupled with synthetic approaches or GM technology, and it is important that the EISBI engages fully with the public and society and acts to lead open debate and promote understanding about the issues.

### *7. Commitments / maturity: which States / Organizations have demonstrated interest / commitment in supporting and/or funding the proposal?*

The original conception of EISBI was developed by scientists in many of the national SB centres established in Europe, formulated in Germany and submitted to ESFRI by Ireland and the UK. Science funding organisations in these countries (BMBF, SFI, BBSRC) are already investing heavily in SB, as are leading agencies in many other European countries. Funding agencies from fifteen countries have formed the ERASysBio consortium to fund joint programmes in SB and develop action at the EU level (Austria, Belgium, Finland, France, Germany, Israel, The Netherlands, Norway, Russia, Slovenia, Spain, Trento-Italy, UK, Luxemburg, Switzerland). Six of these have already established the substantial SysMO programme. ERASysBio has facilitated the coming-together of the directors of the existing substantial SB centres in Europe (there are about 20), together with EMBL/EBI to discuss joint working and the way forward with EISBI. The table below (which is not exhaustive) illustrates the range of organisations which have expressed interest, together with their country and areas of expertise.

| Core Centre | Country | Expertise |
|---|---|---|
| Imperial College; Universities of Manchester, Edinburgh, Nottingham, Oxford, Newcastle | UK | (C M V O CI) |
| Medical University Graz, CEMM, University of Vienna | AT | (C T V O) |
| University of Gent | BE | (V T O) |
| Danish Technical University, University of Copenhagen | DK | (CI O) |
| Institute Marie Curie, Institute Pasteur | FR | (C M V O CI) |
| MPI-MG, MDC, Univ. of Stuttgart, BioQant, EML, DKFZ, HepatoSys | DE | (C T CI M V O) |
| Centre for Systems Biology, Dublin | IE | (CI M O) |
| Weizmann Institute / Tel-Aviv University | IL | (T M O) |
| Netherland Institute of Systems Biology | NL | (CI M O) |
| Systems Biology Research Unit, Barcelona | ES | (M O) |
| Gothenburg Univ., Chalmers University of Technology Sweden | SE | (M V T O) |
| ETH Zürich, Systems X | CH | (T V M O) |
| Academy of Sciences of the Czech Republic | CZ | (C T CI M) |
| EMBL, EBI, | EIRO | (T CI M) |
| BioSim (NoE) | EU | (T CI M) |

Other areas of expertise: C=clinical samples and biobanking, T=experimental technology development, CI=computational infrastructure, M=bioinformatics and computational modelling, V=validation and translation into clinical practice, O=outreach.
Various recent reports have highlighted the need for and timeliness of action in this area including those from ERASysBio (http://www.erasysbio.net), the UK Academy of Medical Sciences and Royal Academy of Engineering (http://www.raeng.org.uk/policy/engagement/pdf/Systems_Biology_Report.pdf) and the ESF (http://www.esf.org/publications/forward-looks.html).

## *8. Costs for construction, operation and decommissioning, indications on project financing Give budget info in Mio €*

| Total preparatory cost | Total construction cost | Operation cost /year | Decommissioning cost |
|---|---|---|---|
| **Total preparatory cost 5 Mio € / 2 years** It is anticipated that the preparatory phase will include decision on pilot implementation, standardisation, harmonising and the planning and preparation of the sources for the EISBI infrastructure. | **Total construction cost 130 Mio €** The work under this category will include: establishing the research infrastructure and facilities; establishing the networking and computing infrastructure – this will largely involve the incorporation of standard hardware, operating systems, specialist software etc. | **Operation cost /year 130 Mio €/year (10 years)** Maintenance and expansion (where necessary) of the information infrastructure. The incorporation of new Institutes and standardisation. Test cases of studies etc. | **Decommissioning cost 0 Mio €** (EISBI will have become self-sustaining) |

## *9. Timetable for construction, operation and decommissioning with duration and possible starting dates.*

**The implementation**: (i) Preparatory phase (year 1 and 2): Problem identification and task definition, (ii) Construction phase (year 3 and 4): Integrating the content; adding/building new

centres, and (iii) Operation phase (year 4 onwards): Problem solutions. In the operation phase (initially 10 years) the centres will approach and solve the identified problems. Additional centres and groups will added to the EISBI, as appropriate. Similarly, over time certain Institutions may be asked to leave the EISBI. The governance of the EISBI will be undertaken by a Governing Board comprising representatives from the Institutions involved in the EISBI, together with industrial and governmental representation.

**Preparatory phase (Detailed)**
Start of preparatory phase: (Start of project)
Establishment of governing board, coordination offices: month 1-3
Establishment of international scientific advisory board: month 1-3
Centre Meeting: representatives of centres expressing interest in participating in EISBI: month 2-4
Funders meeting: representatives of European funding agencies: month 2-4
Selection of participating centres: month 6
Finalisation of implementation plans: month 9-12
Start construction phase with a subset of centres: month 25
All centres actively participating month 36
Full operation: month 49.

| Preparatory phase 3 years | Construction phase 2 years | Operation 10 years (funded phase) | Decommissioning |
|---|---|---|---|

***10. Reference: Person who has submitted the proposal, and will follow up in ESFRI***

This proposal has been assembled by Prof Richard Kitney (Imperial College, London – r.kitney@imperial.ac.uk) drawing heavily on input from other European systems biologists, particularly Hans Westerhoff (Manchester/Amsterdam), Hans Lehrach (MPG) and F.C.Kafatos (Imperial College London). These scientists remain the contact until such time as a formal steering group is established.

# 5 LESSONS LEARNED

## 5.1 Recommendations for resources

The BMS RWG sees an important bottleneck in future sustainable financing of RIs in Europe. BMS RWG recommends that ESFRI should monitor the development of national RI planning to optimise synergy between the ESFRI activities and those of the Member States (MS). Moreover, BMS RWG believes there is a need for significant increase in EU funding, which is essential to provide a catalytic effect and thereby strengthening the European Research Area. Current activities of the EU in wider FP 7 in supporting development of RIs should be continued and reinforced. MS themselves should also increase their funding and develop strategies to ensure the successful progress of the ESFRI RM.

Because of the utmost importance of the RWGs in the whole ESFRI process, the BMS RWG recommends to support these groups. For the incubator role for the RIs on the RM as well as for the evaluation of new RI proposals a RWG desperately needs some funding to keep the whole process going. This is a very low cost compared to the output. Each Chair of a RWG should have two collaborators working on an ESFRI budget, to make the ESFRI process more independent and exclude any possible conflict of interest. The money could come from i) all ESFRI MS, ii) some of the bigger MS, iii) the MS from the Chair originates, and/or iv) the EC.

## 5.2 Recommendations for the process

ESFRI and the ESFRI RM should be instrumental to those RIs that need approval and contributions from several governments (national funding agencies/ research councils) and facilitate the process of obtaining a “go-decision”. ESFRI should be the market place for exchanges and discussions that could lead to joint funding and operation of European RI.

The BMS RWG believes that it is absolutely necessary for the future of ESFRI and a future update of the ESFRI RM, that the existing BMS RWG continues its work with an extended mandate. The BMS RWG sees its main task as reviewing and updating the EU/global scientific landscape and specific needs for RIs in the Life Sciences as well as monitoring the implementation of new RIs. As previously shown, the development of areas like Systems Biology and Synthetic Biology are of utmost importance for the future of the Life Sciences. The support of ESFRI´s incubator role in updating the status of the six BMS RIs already part of the RM, regarding their present technical and scientific development in the pp, will be a mission for the future. In addition the same holds true for the proposals currently recommended for the update of the ESFRI RM when they will enter into their pp, in 2010.

Another goal for the future will be the creation of a mechanism to promote the integration of the old and the new RIs. For the future of Life Sciences RIs it is essential for them to work closely together and address the interfaces and complementarities. Since some of the problems on their pathways to realisation are very similar if not the same, a regular get-together of the scientific coordinators of all RIs on the RM is highly desirable.

With respect to financial resources and to the development of a legal framework the BMS RWG thinks that it is its duty to strengthening the interaction between the ESFRI Infrastructure strategies and the EC Programme Committees (PC). The future RIs, as well as the future projects to be funded by the European Commission, have to follow similar if not the same lines for the sake of the European Research Area.

BMS RWG further would like to express its agreement with the Report of the ERA Expert Group, in which it is stated that ESFRI should stimulate the setting up of specific guidelines for the evaluation of RIs to ensure a more efficient allocation. By doing so, ESFRI should consider the different requirements of the various scientific fields. The different RWGs hold the knowledge about

these requirements and are ideally placed to advise ESFRI in the future.

BMS RWG wishes to stress the importance of regional aspects. The RIs in Life Sciences are mostly multicentred and distributed in nature. This enables the distribution and availability of services across all of Europe, incorporating new MS as well as new fields of research. For this reason BMS RIs would also address the potential of Regional Partner Facilities for enhancing the pan-European scope. The proposed budgets of RIs in Life Sciences also enable easily the participation of smaller MS.

It is the opinion of all RWGs that more time should be available to prepare the next update of the ESFRI RM to more carefully and intensively evaluate the proposals for the update. The evaluation of the proposals should be based on a science-driven advisory scheme through expert boards coming from the respective scientific community, producing independent science-driven advice from a European perspective. The Expert Group members, as well as the RWG members should not have any conflict of interest to guarantee a proper procedure and to avoid the impression that ESFRI is club serving the interests of its members. ESFRI itself could then decide more effectively upon the various proposals on the bases of the knowledge, generated within the scientific community, and of the needs and strategy, as advised by the respective RWG. The ESFRI RM and its credibility is endangered if the whole process is under unreasonable time pressure. The scientific quality deserves as a minimum time a whole year for the assessment of new proposals (receipt of templates to recommendation for update).

BMS RWG hopes that this time ESFRI Forum takes onboard the Lessons Learned that are put forward by the RWGs and acts accordingly in the future for the benefit of European Research Infrastructures.

# GLOSSARY

| | |
|---|---|
| **ANNAEE** | Infrastructure for Analysis and Experimentation on Ecosystems |
| **AS** | Associated States |
| **ASSA** | Advanced Sustainable Sea-based Aquaculture |
| **BBMRI** | Biobanking and Biomolecular Resources Research Infrastructure |
| **BMS RWG** | Biological and Medical Sciences Roadmap Working Group |
| **EATRIS** | European Advanced Translational Research Infrastructure in Medicine |
| **EC** | European Commission |
| **ECRIN-PPI** | European Clinical Research Infrastructures Network |
| **EGLS** | European Group for the Life Sciences |
| **EISBI** | European Integrated Systems Biology Infrastructure |
| **ELIXIR** | European Life-science Infrastructure for Biological Information |
| **EMBRC** | European Marine Biological Resource Centre |
| **ENV RWG** | Environmental Sciences Roadmap Working Group |
| **ERA** | European Research Area |
| **EU-Openscreen** | European Infrastructure of Open Screening Platforms for Chemical Biology |
| **EURAT** | A European Facility for Atmospheric Research |
| **EurIMon** | European Immune Monitoring Platform |
| **Euro-BioImaging** | European Biomedical Imaging Infrastructure – from Molecule to Patient |
| **EUSHAPE** | European Standardisation and Harmonisation Platform for Bio-Medical Research |
| **FASOF** | Free-Air Sites for Ozone Fumigation |
| **FP 5** | 5th Framework Programme |
| **FP 6** | 6th Framework Programme |
| **FP 7** | 7th Framework Programme |
| **High Security Labs** | European High Security BSL4 laboratories building and networking |
| **I3** | Integrated Infrastructure Initiative |
| **IAR** | Individual Assessment Report |
| **IMI** | Innovative Medicine Initiative |
| **INFRAFRONTIER** | European Infrastructure for phenotyping and archiving of model mammalian genomes |
| **INSTRUCT** | Integrated Structural Biology Infrastructure |
| **MS** | Member States |
| **PC** | Programme Committee |
| **PP** | Preparatory Phase |

| | |
|---|---|
| **PSE RWG** | Physical and Engineering Sciences Roadmap Working Group |
| **RI** | Research Infrastructure |
| **RM** | Roadmap |
| **SB** | Systems Biology |
| **SSH RWG** | Social Sciences and Humanities Roadmap Working Group |
| **ToR** | Terms of Reference |

# APPENDIX A LIST OF MEMBERS OF THE BMS RWG

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**Scientific Advisor –** **Fotis Kafatos**

**Secretariat –** **Stefanie Zeretzke (since September 2007)**

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| Turkey | **Kemal Baysal** | Scientific & Technical Research Council of Turkey<br>RIGEB<br>PK21, Gebze, Kocaeli 41470<br>Turkey<br>gmbae@rigeb.gov.tr |
| | **Murat Özgören**<br>(since June 2007) | Department of Biophysics<br>Brain Dynamics Research Center<br>Faculty of Medicine<br>Dokuz Eylul University<br>Balcova<br>35340 Izmir<br>Turkey<br>murat.ozgoren@deu.edu.tr |
| United Kingdom | **Alf Game** | Biotechnology & Biological Sciences Research Council (BBSRC)<br>Polaris House,<br>North Star Avenue<br>Swindon SN2 1UH<br>United Kingdom<br>alf.game@bbsrc.ac.uk |

| Function | Name | Address |
|---|---|---|
| Chair | **Eckhart Curtius** | Federal Ministry of Education and Research<br>Unit 612 Life Sciences – Strategy and Policy Issues<br>53175 Bonn<br>Germany<br>Eckhart.Curtius@bmbf.bund.de |
| Scientific Advisor | **Fotis C. Kafatos** | Division of Cell & Molecular Biology<br>South Kensington Campus,<br>SAF<br>London<br>SW72AZ<br>United Kingdom<br>f.kafatos@imperal.ac.uk |
| BMS Secretariat | **Stefanie Zeretzke** | PT-DLR<br>National Contact Point Life Sciences<br>Heinrich-Konen-Strasse 1<br>53227 Bonn<br>Germany<br>Stefanie.Zeretzke@dlr.de |
| BMS Secretariat | **Jan Skriwanek** | PT-DLR<br>National Contact Point Life Sciences<br>Heinrich-Konen-Strasse 1<br>53227 Bonn<br>Germany<br>Jan.Skriwanek@dlr.de |
| BMS Secretariat | **Marie-Christine Mahlke** | PT-DLR<br>National Contact Point Life Sciences<br>Heinrich-Konen-Strasse 1<br>53227 Bonn<br>Marie-Christine.Mahlke@dlr.de |

# APPENDIX B SUMMARY OF THE MEETINGS

In the frame of the update of the ESFRI Roadmap the BMS RWG met six times. The main issue focussed on the preparation of the BMS report, which should represent on the one hand the actual situation of the ESFRI RI already on the Roadmap and on the other hand the future RI to be included into the Update of the ESFRI Roadmap on the basis of the scientific landscape in the biological and medical sciences. In the following list the meetings and their specific purposes are shown. In addition to the regular BMS RWG meetings, a meeting of the Expert Groups at which the evaluation of the new proposal took place and a meeting of the Coordinators of the already existing RIs in pp took place.

The BMS RWG Secretariat created a password protected working platform and provided it to the BMS RWG members in November 2007. All members received access to this platform, which contains all documents the group created (all agendas and minutes of the meetings, the new proposals, the assessment forms, the draft of the BMS report etc.) and which was kept by the BMS RWG Secretariat, to guarantee the transparency of the process.

| Date | Title | Purpose |
|---|---|---|
| 04th & 05th Oct. 2008 | 09th BMS RWG meeting, London | • Discussion on the procedure on preparing the update of the ESFRI Roadmap 2008-04-30<br>• Discussion on methods to access the new proposals for updating the Roadmap as well as approving experts for the evaluation procedure<br>• Discussion on the already received proposals for the update of the Roadmap<br>• Agreement on the timetable to prepare the 1st Draft of the BMS Report |
| 13th Dec. 2008 | 10th BMS RWG meeting, Nicosia | • Discussion on the status and further ongoing of the procedure on preparing the update of the ESFRI Roadmap 2008<br>• Discussion / work on the new proposals |
| 14th Jan. 2008 | BMS Expert Group meeting, Berlin | • Discussion / work on the BMS proposals for the update of the ESFRI Roadmap 2008<br>• Formulation of a final conclusion for a recommendation towards the BMS RWG |
| 24th & 25th Jan. 2008 | 11th BMS RWG meeting, Jerusalem | • Discussion on the BMS Scientific Landscape<br>• Finalisation of the evaluation of the received proposals |
| 31st Mar. & 01st Apr. 2008 | 12th BMS RWG meeting, The Hague | • Discussion on the new BMS proposal in Systems Biology<br>• Discussion on the draft of the BMS report and the scientific landscape |

| Date | Title | Purpose |
|---|---|---|
| 11th Jun. 2008 | BMS project coordinators meeting, Brussels | • Exchange of Experience |
| 11th & 12th Jun. 2008 | 13th BMS RWG meeting, Brussels | • Final decision on the new BMS proposals in Systems Biology and Chemical Biology<br>• Finalisation of the BMS report and the scientific landscape |
| 01st & 02nd Oct. 2008 | 14th BMS RWG meeting, Crete | • Discussion on the ESFRI Updated Roadmap<br>• Future of the RWG<br>• Progress of the Systems Biology proposal |

# APPENDIX C LIST OF PROPOSALS ALREADY ON THE ESFRI ROADMAP IN PP

| No. | Title | Acronym | Coordinator | Duration of the PP in Months |
|---|---|---|---|---|
| 1 | Biobanking and Biomolecular Resources Research Infrastructure | BBMRI | Univ. Prof. Dr. Kurt Zatloukal (Austria) Kurt.zatloukal@meduni-graz.at | 27 |
| 2 | European Advanced Translational Research Infrastructure in Medicine | EATRIS | Prof. Dr. Rudi Balling (Germany) rudi.balling@helmholtz-hzi.de | 36 |
| 3 | European Clinical Research Infrastructures Network and biotherapy facilities | ECRIN | Prof. Jacques Demotes-Mainard (France) demotes@tolbiac.inserm.fr | 36 |
| 4 | European Lifescience Infrastructure for Biological Information | ELIXIR | Prof. Janet Thornton (United Kingdom) thornton@ebi.ac.uk | 38 |
| 5 | European Infrastructure for phenotyping and archiving of model mammalian genomes | INFRAFRONTIER | Prof. Dr. Martin Hrabé de Angelis (Germany) hrabe@helmholtz-muenchen.de | 36 |
| 6 | Integrated Structural Biology Infrastructure | INSTRUCT | Prof. David I Stuart (United Kingdom) instruct@strubi.ox.ac.uk | 24 |

# APPENDIX D LIST OF PROPOSALS RECEIVED AND ASSESED

**List of proposals provided to BMS RWG for assessment**

| No. | Title | Acronym | Scientific Area | Submitted by |
|---|---|---|---|---|
| RU01 | European high security BSL4 laboratories building, upgrading and networking | BLS4 | High Security Laboratories | France |
| RU02 | European Integrated Systems Biology Infrastructure | EISBI | Systems Biology | Ireland, United Kingdom |
| RU04 | European Infrastructure of Open Screening Platforms for Chemical Biology | EU-Openscreen | Chemical Biology | Germany |
| RU05 | European Immune Monitoring Platform | EurIMon | Infectious Diseases | Germany |
| RU16 + RU41 | European Biomedical Imaging Infrastructure - from Molecule to Patient | Euro-BioImaging | Imaging | Switzerland, Austria |
| RU18 | European Standardisation and Harmonisation Platform for Bio-Medical Research | EUSHAPE | Infectious Diseases | Germany |
| RU22 | European Marine Biological Resource Centre | EMBRC | Biological Sciences | Italy |

**List of proposals provided to ENV and BMS RWG for assessment**

| No | Title | Acronym | Area | Submitted by |
|---|---|---|---|---|
| RU30 | Advanced Sustainable Sea-based Aquaculture: Integrat-ing aquaculture knowledge and technology through the new large-scale Research Infrastructure ACE | ASSA | BMS Proposals for ENV consid-eration | Norway |

### List of ENV proposals received for BMS consideration

| No | Title | Acronym | Area | Submitted by |
|---|---|---|---|---|
| RU23 | Eurat Observatory: A European Facility for Atmospheric Research | EURAT | ENV Proposals for BMS consideration* | Italy |
| RU25 | Free-Air Sites for Ozone Fumigation (FASOF) for a scientifically-sound legislation to protect European vegetation against ozone | FASOF | ENV Proposals for BMS consideration* | Italy |
| RU32 | Infrastructure for Analysis and Experimentation on Ecosystems | ANNAEE | ENV Proposals for BMS consideration* | France |

*** not assessed by BMS because out of the BMS scope**

### List of e-IWG proposals received for BMS consideration

| No. EC | Full Name | Abbreviation | Area | Submitted by |
|---|---|---|---|---|
| RU17 | A European Nexus & Network for Exploration Using Simulation in Science | CECAM | e-IWG Proposals for BMS consideration | Ireland |
| RU31 | European Software Services Network for Large-Scale Research Facilities | Software Service | e-IWG Proposals for BMS consideration | Finland |
| RU33 | Infrastructure for Preservation of Unrevealed Scientific Data | IPURE | e-IWG Proposals for BMS consideration | Finland |

# APPENDIX E MEMBERS OF THE BMS EXPERT GROUPS

| | |
|---|---|
| Aperia, Anita | Karolinska Institutet, Stockholm, Sweden |
| Arendt, Detlev | EMBL Heidelberg, Germany |
| Balling, Rudi | Helmholtz Centre for Infection Research, Braunschweig, Germany |
| Beem, Edvard | The Netherlands Organisation for Health Research and Development ZonMw, The Hague, Netherlands |
| Do Rosário, Virgílio | University Nova de Lisboa, Portugal |
| Frøkjær, Jørgen | University of Aarhus, Denmark |
| Garside, Paul | University of Strathclyde Glasgow, United Kingdom |
| Keane, Joseph | Trinity College Dublin, Ireland |
| Malas, Stavros | The Cyprus Institute of Neurology and Genetics, Nicosia, Cyprus |
| Mlinarič-Raščan, Irena | University of Ljubljana, Slovenia |
| Osborn, Mary | Max Planck Institute for Biophysical Chemistry, Göttingen, Germany |
| Pastore, Annalisa | MRC National Institute for Medical Research, London, United Kingdom |
| Pihlajaniemi, Taina | University of Oulu, Finland |
| Samarut, Jacques | Genomics Rhône-Alpes Genopole Lyon, France |
| Syková, Eva | Institute of Experimental Medicine ASCR, Prague, Czech Republic |
| Ter Meulen, Jan | Merck Research Laboratories, West Point, USA |
| Thanos, Dimitrios | Academy of Athens, Greece |
| Zouros, Eleftherios | University of Crete, Greece |

# APPENDIX F LITERATURE

EGLS (European Group on Life Sciences), January 2005, List of challenges for the future

ERASysBio ERA-NET for Systems Biology, November 2007, Systems Biology in the European Research Area

European Commission, 2007, Synthetic Biology A NEST Pathfinder Initiative, ISBN 92-79-03832-X

European Commission, Report of the ERA Expert Group, 2008, Developing World-class Research Infrastructures for the European Research Area (ERA), ISBN No. 978-92-79-2008312-9

European Science Foundation, August 2007, Systems Biology: a Grand Challenge for Europe

OECD (Organisation for Economic Co-Operation and Development) Report, March 2001, Underpinning the Future of Life Sciences and Biotechnology, ISBN No. 92-64-18690-5

The Academy of Medical Sciences and The Royal Academy of Engineering, February 2007, Systems Biology: a vision for engineering and medicine, ISBN No. 1-904401-13-5