



Publishable Summary

The INFRAFRONTIER mission: *“To build a world-class research infrastructure that provides the biomedical research community with the tools needed to unravel the role of gene function in human disease.”*

World-class resources and services

Mouse models have become a **central asset in the functional analysis of our genes**. The mouse genome is fully sequenced. 99% of the coding genes present in man are also present in the mouse. In the last two decades researchers have developed an extensive toolbox to study the functional effects of genetic variation in the mouse. The technology to alter the mouse genome in a targeted way (knock-out mice) earned its originators the **Nobel Prize** in the year 2007.

Mouse models are also central in the **study of human diseases**. Mice and humans share the majority of disease related genes. The susceptibility of mice to targeted genetic intervention makes them the ideal model organism for the study of gene function in health and disease. As a result, mice are today the most widely used animal model in biomedical research.

Currently, hundreds of new mouse lines are generated each year in biomedical research laboratories around the globe. This creates an **enormous demand** for:

Systemic Phenotyping

Systemic phenotyping is the comprehensive functional and molecular characterisation of mouse lines in all relevant organ systems and disease areas. The **mouse clinics** partnering in INFRAFRONTIER use cutting-edge technologies, among them the latest in vivo imaging techniques and non-invasive methods, to reveal the role of the genes and environment on development, morphology, physiology, metabolism, behaviour and pathology. The efficient use of modern analytic technology and data management tools provides novel insights into gene function and creates basis for new therapeutic approaches and disease prevention strategies.

Archiving and Distribution

Keeping live mice on shelf for extended periods is not only costly, it also bears the risk of losing biologically relevant phenotypes due to genetic drift or disease, and it is not desirable for animal welfare reasons. **Mouse repositories therefore preserve scientifically valuable mouse models** and distribute them to upon request to the biomedical research community.

EMMA - The European Mouse Mutant Archive is the leading mouse repository in Europe and important partner in the global network of mouse archives. EMMA offers archiving and distribution of mouse models under highest quality standards and access to the strain data in the EMMA resource database. An additional specialized service of EMMA is the generation of germ-free (axenic) mice.

The scope of the INFRAFRONTIER Preparatory Phase

The Preparatory Phase of INFRAFRONTIER lasted from March 2008 to December 2012. It was coordinated at the Helmholtz Zentrum München by Prof. Martin Hrabé de Angelis. It aimed at resolving the main financial and organisational issues required for implementing a sustainable pan-European INFRAFRONTIER Research Infrastructure for systemic phenotyping, archiving and distribution of mouse models of human diseases:

- **Capacity building** based on sustainable funding to meet the increasing demand for systemic phenotyping, archiving and distribution;
- Developing a **business plan** based on a sustainable funding concept;
- Identification of the most suitable **legal form**;
- Providing a **strategic plan** for the implementation phase; and
- Reaching a **legal agreement** between all partners.

The INFRAFRONTIER preparatory phase addressed these issues in its different work packages. The overall strategy and governance of the planned infrastructure is covered in **WP2 - Strategy and Governance**. Assessing the best legal form is tasked to **WP3 - Legal Work**. The development of the business plan and a sustainable funding concept is carried out in **WP4 - Financial Work**. The propagation and advancement of knowledge and standards within the consortium is achieved through **WP5 - Draft Engineering Specifications**, **WP6 - Training** and **WP7 - Bioinformatics**. The overall consortium management, including the communication among the consortium members is carried out by **WP1 - Management** which is supported by **WP8 - Networking** to communicate with INFRAFRONTIER's external stakeholders.

At the end of its Preparatory Phase, the INFRAFRONTIER project has fully achieved its goals for the implementation of the INFRAFRONTIER Research Infrastructure: Supported by the **INFRAFRONTIER Inter-Ministry Working Group**, the **Memorandum of Understanding** by the founding members have been signed and the legal documents have been prepared **to establish the INFRAFRONTIER Legal Entity** in early 2013.

The INFRAFRONTIER consortium

The INFRAFRONTIER Preparatory Phase project brought together 28 partners from twelve European countries and Canada. The scientific partners are the leading research facilities in the field of systemic phenotyping, archiving and distribution of mouse models. The administrative partners represent national research ministries and funding agencies:

Scientific partners

- **Helmholtz Zentrum München - German Research Center for Environmental Health, GmbH (HMGU)**, Prof. Martin Hrabé de Angelis (INFRAFRONTIER Coordinator), Neuherberg/München, Germany
- **MRC Mammalian Genetics Unit (MRC-MGU)**, Prof. Steve Brown, Harwell, UK
- **Consiglio Nazionale delle Ricerche - Institute of Cell Biology (CNR-IBC)**, Prof. Glauco Tocchini-Valentini, Monterotondo/Rome, Italy
- **Centre Européen de Recherche en Biologie et en Médecine GIE (CERBM-GIE)**, Dr. Yann Héroult, Illkirch/Strasbourg, France

- **Genome Research Limited (Sanger)**, Dr. Ramiro Ramirez-Solis, Hinxton, UK
- **Biomedical Sciences Research Center Alexander Fleming (Fleming)**, Prof. George Kollias, Vari/Athens, Greece
- **Karolinska Institute (KI)**, Prof. Urban Lendahl, Stockholm, Sweden
- **Fundação Calouste Gulbenkian (FCG-IGC)**, Dr. Jocelyne Demengeot, Oeiras, Portugal
- **CNRS Institute de Transgenose (INTRAGENE)**, Dr. Yann Hérault, Orléans, France
- **Universidad Autònoma de Barcelona (UAB)**, Prof. Fatima Bosch, Barcelona, Spain
- **Centro Nacional de Biotecnologia (CNB-CSIC)**, Dr. Lluís Montoliu, Madrid, Spain
- **University of Oulu (UOULU)**, Prof. Taina Pihlajaniemi, Oulu, Finland
- **European Molecular Biology Laboratory (EMBL-EBI)**, Dr. Ewan Birney, Hinxton, UK
- **Helmholtz Centre for Infection Research GmbH (HZI)**, Prof. Klaus Schughart, Braunschweig, Germany
- **University of Copenhagen (KU-TCF)**, Prof. Cord Brakebusch, Copenhagen, Denmark
- **Institute of Molecular Genetics of the Czech Academy of Sciences / Czech Centre for Phenogenomics (IMG, BIOCEV)**, Dr. Radislav Sedlacek, Czech Republic
- **University of Veterinary Medicine Vienna, Biomodels Austria (Biat)**, Prof. Thomas Rüllicke, Vienna, Austria
- **Centre for Phenogenomics (TCP)**, Dr. Colin McKerlie, Toronto, Canada
- **INSERM Centre for Immunogenomics (CIPHE)**, Dr. Bernard Malissen, Marseille, France

Ministries and research councils

- **Medical Research Council (MRC)**, United Kingdom
- **Centre National de la Recherche Scientifique (CNRS)**, France
- **Consejo Superior de Investigaciones Científicas (CSIC)**, Spain
- **Hellenic Republic Ministry of Development (HRMD)**, Greece
- **Helmholtz Association (Helmholtz)**, Germany
- **German Ministry for Research and Education (BMBF)**, Germany
- **Swedish Research Council (SRC)**, Sweden
- **Generalitat de Catalunya, Departament de Salut (GENCAT)**, Spain
- **Parque Científico de Madrid (FPCM)**, Spain
- **Comunidad de Madrid, Dirección General de Universidades e Investigación (DGUI)**, Spain
- **Ministry of Education, Youth and Sports, Czech Republic (MEYSCR)**, Czech Republic
- **Institut National de la Santé et de la Recherche Médicale (INSERM)**, France
- **Ministry of Labour Health and Social Policies (Health Sector) General Directorate Health Research (ITMOH)**, Italy

The INFRAFRONTIER Research Infrastructure - Added value for Europe

The INFRAFRONTIER Preparatory Phase lead to a new infrastructure that will ensure the appropriate coverage of phenotyping and archiving capacities in the **European Research Area**. INFRAFRONTIER will place Europe in a leading position in the worldwide competition for resources and knowledge for medically relevant mouse models.

The INFRAFRONTIER Research Infrastructure will facilitate the high throughput systemic phenotyping and cryopreservation of mouse mutants to make the most efficient use of the emerging resources resulting in the provision of new mouse disease models for the biomedical research community. This will speed up the discovery of molecular mechanisms of diseases and health, an important step for the future of molecular medicine and the advancement of diagnosis and therapy.

Results of the first reporting period (March 2008 to February 2009)

The activities of the INFRAFRONTIER preparatory phase were initiated at the **INFRAFRONTIER Kick-off Meeting** in May 2008.

At the **Strategy Meeting** that took place in July 2008 the consortium partners started to draft a comprehensive description of the overall strategy and the governance of the infrastructure in operation. This involves the definition and agreement on the decision making processes, the planned services and the access and participation rules of the infrastructure. The outcome was summarised in a **Draft Strategic Plan** which served as a reference for further activities.

In order to identify the best legal form for INFRAFRONTIER, the project office organised a **Joint Workshop of the Biomedical (BMS) Research Infrastructures on the ESFRI Roadmap**, to discuss suitable legal instruments with the other preparatory phase projects of the biological and medical section (BMS) of the ESFRI roadmap in November 2008. A **dedicated lawyer** was employed in January 2009 to lead and drive the assessment of legal forms.

A further objective of the BMS Workshop in November 2008 was to discuss **dedicated funding instruments for research infrastructures provided by the European Investment Bank (EIB)**. The financial planning at the national level was assessed in a **Funding Query** in which the consortium partners were asked to provide information about their projected requirements for construction and operation and about financial commitments they already received from European (e.g. Structural Funds), national or institutional funding sources.

At a workshop in Braunschweig in September 2008 the approach and work program of a **Visiting Team** consisting of INFRAFRONTIER experts in the fields of animal facility management and the operational management of phenotyping and cryo-preservation units, together with an external architect specialised in the planning of animal facilities was put together.

Dedicated **training courses** for phenotyping and for cryopreservation were held in January and February 2009, to propagate knowledge and standards within the consortium and from the experienced members to staff of the emerging facilities. A total of 34 participants from Greece, Finland, Czech Republic, Spain, Portugal, Denmark and France received training.

To provide information about the project, both for the internal and external stakeholders, the **INFRAFRONTIER web portal (www.INFRAFRONTIER.eu)** was established. The results of a literature study to identify potential new members was summarised in the **Report on the Identification of New Partners**. The Coordinator, the project manager, and members of the project consortium represented INFRAFRONTIER at a number of relevant scientific conferences and meetings with the European Commission, ESFRI, the ESFRI BMS projects and other stakeholders.

Results of the second reporting period (March 2009 to February 2010)

At the first **INFRAFRONTIER Annual Meeting** in April 2009 all project activities were summarised and reviewed. In December 2009 the EC signed an **amendment to the grant agreement** of INFRAFRONTIER. With this amendment six new members from Czech Republic, Austria, Canada, France and Italy were included in the INFRAFRONTIER Consortium. This documents the growing significance of INFRAFRONTIER both in the new EU member states and in the global scientific community.

The strategic plan for the implementation of INFRAFRONTIER received a major update at the **INFRAFRONTIER Scientific Strategy Meeting** in September 2009. Closely connected to the overall strategy are the development of a sustainable funding concept, and the assessment of the best legal status for the INFRAFRONTIER Research Infrastructure. A dedicated **ESFRI BMS Workshop** in March 2009 reviewed financial, legal and organisational strategies of different existing European and global research infrastructures. On the basis of this meeting and the previous one in November 2008 a **Report on Survey of Funding Strategies of Resources Centres** was drafted.

Different legal forms for research infrastructures were scrutinised, an assessment of legal forms was presented at the Annual Meeting 2009 and formalised in a **Report on Assessment and Recommendation of the Best Legal Status** for the Scientific Strategy Meeting in September 2009.

The results of the **Funding Query** among the INFRAFRONTIER partners carried out in early 2009 were presented at the first Annual Meeting in April 2009. This top-down approach was complemented by a bottom-up **Analysis of Costs**, taking into account the costs of the different activities in the INFRAFRONTIER Research Infrastructure and the projected European demand for these services.

These cost analyses form part of the **Draft Business Plan**, which was completed in April 2010, together with the **Draft Statutes, Draft Procurement Rules** and the **Draft Memorandum of Understanding** for the INFRAFRONTIER Research Infrastructure.

Based on a series of **site visits** carried out between February and November 2009 and a dedicated **WP5 Workshop** in September 2008 and March 2010 a **Report on Draft Engineering Specifications** was completed in spring 2010. A **training course** for archiving was held in March 2009. Two extensive bioinformatics surveys were initiated in April 2009, the first on **Cryo sample repository management systems (CSRMS)**, the second on **Animal husbandry management systems and laboratory information management systems (AMS & LIMS)**. The networking and outreach activities included the presentation of INFRAFRONTIER project at a scientific events and dedicated meetings organised by the European Commission and other important stakeholders, the production of information material and dedicated articles and publications and the production, online distribution and analysis of a **user survey questionnaire**.

Results of the third reporting period (February 2010 to March 2012)

During the third reporting period INFRAFRONTIER made important progress towards reaching the goal of implementing the pan-European INFRAFRONTIER Research Infrastructure. The establishment of the **INFRAFRONTIER Inter-Ministry Working Group** was a key step to ensure involvement of the Member States and to obtain their input on strategy and governance.

The Working Group was established in October 2010 and had further meetings in January 2011, October 2011 and February 2012. During these meetings the legal documents produced by WP3 for implementing the INFRAFRONTIER Legal entity were discussed and refined. The signing of the **Memorandum of Understanding** for setting up the pan-European INFRAFRONTIER Research Infrastructure by the first Member States was accomplished in May 2011.

The project made significant progress towards ensuring financial sustainability for the national research infrastructure components. **136 Mio € have been secured for the construction, upgrade and operation** of the national components in Germany, France, Czech Republic, Italy, Finland, Greece, Austria and Spain.

As part of its networking and outreach activities, INFRAFRONTIER organised a **EuroMouse 2012 Meeting** with the title **European Mouse Resources for clinical and translational research**. 70 participants from 36 institutions in 19 countries participated.

Together with the ESFRI BMS Group, INFRAFRONTIER published the **Strategy Paper of the BMS research infrastructures** and the **Position Paper on the Common Strategic Framework**. INFRAFRONTIER was presented and promoted at scientific meetings. The coordinator and the project manager held close contact to the European Commission, the ESFRI BMS projects, the other ESFRI projects and INFRAFRONTIER related EC projects at numerous events.

An **Archiving Training Course** was held in December 2010 in Paris. Two training sessions for mouse phenotyping were held: a **Phenotyping Training Course** took place in February 2011 in Strasbourg and Neuherberg/Munich; a **Phenotyping Training Event** took place in February 2012 in Strasbourg.

The results of the site visits carried out during reporting period 1 and 2 lead to the generation of the detailed **WP5 report on draft engineering specifications**. In addition, a specification of technical modules for genotyping and archiving facilities was developed and described in detail in the **Report on technical modules for genotyping and archiving facilities**. The results of the work package on technical engineering were presented at three different scientific conferences and were accepted for publication in the Journal of the American Association for Laboratory Animal Science.

Information on the project status was continually updated in the external and internal sections of the INFRAFRONTIER web portal (www.infrafrontier.eu). The results of a survey on existing IT systems in mouse facilities are summarised in two reports: **Survey on cryo sample repository management systems (CSRMS)** and **Report on Survey on Animal Husbandry Management Systems (AMS) and Laboratory Information Management Systems (LIMS)**. The **Report on a common nomenclature for master data of mutant mouse lines** summarises the analysis of existing nomenclature for master data in the context of large-scale mouse production, phenotyping, archiving and distribution. Data integration across databases for large-scale mouse projects is summarised in a **Report detailing recommendations for standards underlying the integration of the EMMA, EuroPhenome and EUComm databases**.

Results of the fourth reporting period (March 2012 to December 2012)

The main focus of the fourth reporting period of the INFRAFRONTIER Preparatory Phase project was to **finalise the legal documents** for the implementation of the INFRAFRONTIER Research Infrastructure. On the basis of the (i) **Memorandum of Understanding** signed by all designated founding members (DE, FR, CZ, FI, GR, EMBL), (ii) the **Businessplan**, and (iii) the **Strategic Plan for the Implementation of the INFRAFRONTIER Research Infrastructure**, the **Articles of Association of the INFRAFRONTIER GmbH** with seat at the Helmholtz Zentrum München, Germany were finalised in the **INFRAFRONTIER Inter-Ministry Working Group**.

Two more reports, the first on **Intellectual Property Issues in the INFRAFRONTIER Research Infrastructure**, the second on the **Integration of New Partners**, summarise the activities during the INFRAFRONTIER Preparatory Phase in these two important areas.

A further important activity of the fourth reporting period was to initiate the **reconstruction of the INFRAFRONTIER web page** to reflect the progression from the Preparatory Phase to the operational stage. This includes the implementation of a content management system, a complete **re-write of content**, the **implementation of new functionality** for providing user access to the resources and services of the INFRAFRONTIER Research Infrastructure, the **integration of the existing EMMA website**, and the move of the INFRAFRONTIER website to the servers of the European Bioinformatics Institute. A professional web design agency was hired to aid in this process.

With the imminent **establishment of the INFRAFRONTIER GmbH** in early 2013, right after the end of the INFRAFRONTIER Preparatory Phase, the project has fully achieved its goals. Moreover, a prolonged transition phase without stable legal arrangements, as seen in some other ESFRI projects, could be avoided. Finally, the preparations for the application for an **Infrafrontier ERIC** are on its way, in order to proceed once the legal requirements for setting up the ERIC have been created in all INFRAFRONTIER Member States.