InfraCoMP - Coordinating the cooperation of the ESFRI project INFRAFRONTIER with the International Mouse Phenotyping Consortium (IMPC)

1.1 Concept and objectives

The aim of the InfraCoMP project is to provide a coordination mechanism between the pan-European ESFRI research infrastructure INFRAFRONTIER and the International Mouse Phenotyping Consortium (IMPC). InfraCoMP is coordinated by Prof. Martin Hrabé de Angelis from the Helmholtz Zentrum München, Germany. The Helmholtz Zentrum München is also the seat of the INFRAFRONTIER GmbH, Prof. Hrabé de Angelis is one of its Directors.

The INFRAFRONTIER Research Infrastructure (www.infrafrontier.eu) offers access to resources and services related to mouse models to study human diseases. In particular, INFRAFRONTIER offers access to the comprehensive analysis of gene mutations on the whole organism (the so-called systemic phenotyping) in the INFRAFRONTIER mouse clinics, and to the archiving and distribution of scientifically valuable mouse lines in EMMA - the European Mouse Mutant Archive.

The IMPC (www.mousephenotype.org) is a global project to carry out systemic phenotyping of knockout mutants for each of the approximately 20,000 protein coding mouse genes. This will allow to create a the first comprehensive catalogue of gene function in health and disease.

Both, INFRAFRONTIER and the IMPC are rooted in successful European initiatives funded by the EC framework programmes, specifically EUMORPHIA, EUMODIC, EUCOMM and EMMA. The scope of INFRAFRONTIER and IMPC is different, yet complementary: INFRAFRONTIER aims to provide a sustainable research infrastructure that provides the biomedical research community with access to systemic phenotyping, archiving and distribution of mouse models; The IMPC proposes an ambitious project plan, utilising the research infrastructure provided by INFRAFRONTIER in Europe and similar resources around the globe.

INFRAFRONTIER and the IMPC have many common issues and face similar challenges; InfraCoMP provides an effective coordination mechanism between the two, building on the fact that many INFRAFRONTIER partners are also members of the IMPC.

To do so, InfraCoMP brings together all the relevant players in INFRAFRONTIER and the IMPC in regular workshops to discuss common approaches and strategies in four main areas:

- Topic 1 - Mouse phenotyping
- Topic 2 - Mouse production, archiving and distribution
- Topic 3 - Access to phenotyping data, and
- Topic 4 - Community Engagement

The discussions in these workshops aid to accommodate the requirements of the European biomedical research community addressed by INFRAFRONTIER with the objectives of the IMPC, to ensure an effective cooperation and to avoid duplication of efforts. The workshop results are put on record in dedicated meeting reports, which are being made available through the INFRAFRONTIER website.

1.2 InfraCoMP partners

The InfraCoMP partners are the INFRAFRONTIER institutions that carry out systemic phenotyping or are currently building mouse clinics, and the European Bioinformatics Institute. All are either already IMPC partners or intend to become partners once their phenotyping facilities become operable. All of them, except the partners from Barcelona and Toronto are also archiving and distribution centres of mouse lines in EMMA - the European Mouse Mutant Archive.

- **Helmholtz Zentrum München - German Research Center for Environmental Health, GmbH (HMGU)**, Prof. Martin Hrabé de Angelis (INFRAFRONTIER Coordinator), Neuherberg/München, Germany
- **Centre Européen de Recherche en Biologie et en Médecine GIE (CERBM-GIE)**, Dr. Yann Hérault, Illkirch/Strasbourg, France
- **MRC Mammalian Genetics Unit (MRC-MGU)**, Prof. Steve Brown, Harwell, UK
- **Genome Research Limited (Sanger)**, Dr. Ramiro Ramirez-Solis, Hinxton, UK
- **Centre for Phenogenomics (TCP)**, Dr. Colin McKerlie, Toronto, Canada
- **Universidad Autònoma de Barcelona (UAB)**, Prof. Fatima Bosch, Barcelona, Spain
- **Consiglio Nazionale delle Ricerche**, Prof. Glauco Tocchini-Valentini, Monterotondo/Rome, Italy
- **Institute of Molecular Genetics of the Czech Academy of Sciences / Czech Centre for Phenogenomics (IMG, BIOCEV)**, Dr. Radislav Sedlacek, Czech Republic
- **European Molecular Biology Laboratory (EMBL-EBI)**, Dr. Helen Parkinson, Hinxton, UK

The non-INFRAFRONTIER IMPC partners are represented in InfraCoMP on the level of the **International Steering Committee** and can thus provide input to the organisation of the InfraCoMP Workshops.

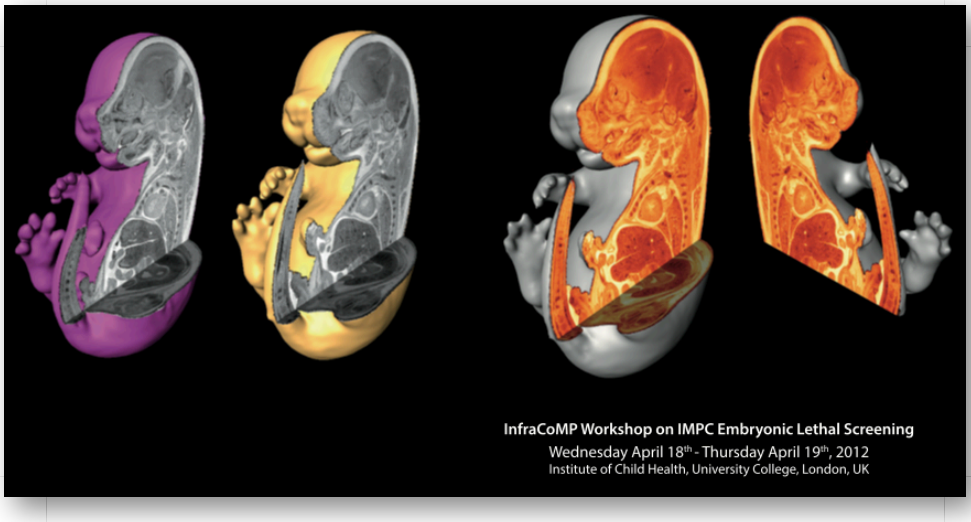
1.3 Results of the first reporting period

During the first reporting period, InfraCoMP organised three international workshops:

The **InfraCoMP Kick-Off Meeting** in Freising close to Munich, Germany in November 2011, attended by 77 international participants, served to initiate the project activities and to foster in-depth discussions on the availabilty of ES cells from the EUCOMM and KOMP resources, mouse production strategies and on the IMPC adult phenotyping pipeline including the experimental control scheme.

The participants of the InfraCoMP Kick-Off Meeting

The **InfraCoMP Workshop on IMPC Embryonic Lethal Screening** in London, UK in April 2012, attended by 110 international participants, focused on the development of a framework for the phenotyping of embryonic lethal mutations in the context of the IMPC. The results of the workshop were published in the May 2013 issue of the journal 'Disease Models & Mechanisms'.



Meeting announcement for the InfraCoMP Workshop on IMPC Embryonic Lethal Screening

The **INFRAFRONTIER / IMPC Korea Meeting** on Jeju Island, Korea in September 2012, attended by 70 international participants, focused on Asian national and transnational programs for mouse production, systemic phenotyping, archiving and distribution. The meeting highlighted Asia's important position in the global effort to functionally annotate the entire mammalian genome and provided information on current issues and activities of mouse phenotyping in Asia, and how these activities integrate with INFRAFRONTIER and the IMPC.

The participants of the INFRAFRONTIER / IMPC Korea Meeting

1.4 Results of the Second Reporting Period

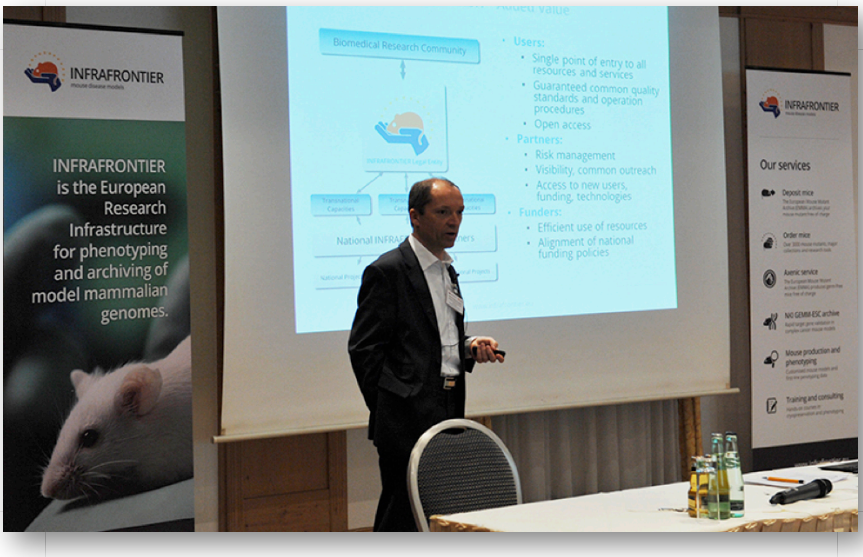
During the second reporting period, InfraCoMP organised three international workshops, one of these workshops was split into two meetings with complementary thematic focus on two different locations:

The **INFRAFRONTIER / IMPC / IKMC Rome Meeting** in Rome, Italy in December 2013 was a large meeting primarily focused on reaching out to the scientific user communities of INFRAFRONTIER and IMPC and the International Knockout Mouse Consortium (IKMC). The meeting was attended by more than 200 participants and showed that the INFRAFRONTIER / IMPC / IKMC resources are already widely used in different research communities. In order to fully exploit the wealth of mouse phenotyping data available, further efforts are required to harmonise general approaches, better bioinformatics tools for data integration are required, and generally existing communication efforts should be intensified.

Prof. Martin Hrabě de Angelis opens the INFRAFRONTIER / IMPC / IKMC Rome Meeting

The **INFRAFRONTIER / IMPC Workshop - Promoting the International Exchange of Mouse Mutant Resources** was held in May 2014 in Munich, Germany, it was attended by 65 international participants. The main objective of the workshop was to facilitate the international exchange of mouse resources. This included discussions on how to simplify licences and material transfer agreements and how to facilitate resource sharing with industry. Also the technical underpinnings of resource sharings and the implications of the novel gene-editing methodologies were discussed. The meeting was covered in an editorial by Nature.

The **INFRAFRONTIER / IMPC Phenotyping Workshop 2014** and the **INFRAFRONTIER / IMPC Statistical Technical Working Group Meeting** were two complementary meetings held in San Francisco, USA in March 2014 and in Hinxton, UK in July 2014. The Phenotyping Workshop was attended by 60 international participants to discuss the performance of the different tests in the IMPC phenotyping pipeline and to initiate the formulation of the IMPC pipeline for phase II. The statistical working group meeting was attended by 20 international participants to discuss large-scale analysis of high-throughput phenotyping data.



Prof. Martin Hrabě de Angelis at the INFRAFRONTIER Repository Workshop.

1.5 Overall Impact

The International Mouse Phenotyping Consortium is an ambitious global endeavour to create a **comprehensive catalogue of gene function in human health and disease**. The IMPC uses a systematic approach of generating and phenotyping knock-out mice for every mammalian gene to provide **disease relevant knowledge** for all genes in the human genome. It is the role of the continental research infrastructures (**INFRAFRONTIER** in Europe, **KOMP, NorComm** in America, **RIKEN, CARD** in Asia) to provide access to the resources created by the IMPC.

Europe considerably contributes to overall IMPC effort, to date 48% of the knock-out mice generated in the IMPC are provided by European partners. The **European Mouse Mutant Archive**, which is the mouse repository component of **INFRAFRONTIER**, has the crucial role of distributing these lines to the global research community.

Global distribution of IMPC mouse lines by INFRAFRONTIER.

The **InfraCoMP project** provided a vital mechanism to emphasise the important role of the European INFRAFRONTIER / IMPC partners in the IMPC and to strengthen Europe in defining its overall scientific strategy:

- InfraCoMP was pivotal for defining the **IMPC strategy for embryonic phenotyping**, which was developed in the *InfraCoMP Workshop on IMPC Embryonic Lethal Phenotyping* and publicised in the **Bloomsbury Report**: *Adams et al. 2013 - Bloomsbury report on mouse embryo phenotyping. Dis Model Mech. 2013 May; 6(3):571–9. doi: 10.1242/dmm.011833. Epub 2013 Mar 18*.
- InfraCoMP provided the forum for **regular scientific reviews** of IMPC mouse production strategies, the adult phenotyping pipeline, statistics and control schemes and the data analysis strategy.
- InfraCoMP had a strong focus on **outreach to the scientific communities**, particularly the emerging communities in Asia (*INFRAFRONTIER / IMPC Korea Meeting*) and the clinical and translational research communities (*INFRAFRONTIER / IMPC / IKMC Rome Meeting*).
- InfraCoMP promoted the **simplification of the international exchange of mouse resources** in the I*NFRAFRONTIER / IMPC Mouse Repository Workshop*, which was also featured in a **Nature Editorial**: *Alison Abbott - Still much to learn about mice. Nature. 2014 May 22; 509(7501):399. PMID 24860878*.