



# Minutes of the InfraCoMP Kick-Off Meeting

Munich Airport Marriott Hotel, Freising, 14-15 November 2011



## I. Participants

### 1 - Infrafrontier/InfraCoMP Partners

#### Helmholtz Zentrum München, Germany

Blasius, Karina  
de Castro, Ana  
Fuchs, Helmut  
Gailus-Dumer, Valérie  
Hagn, Michael  
Hrabé de Angelis, Martin  
Marschall, Susan  
Raess, Michael  
Rossbacher, Jörg  
Wurst, Wolfgang

#### ICS – Mouse Clinical Institute, France

Herault, Yann  
Selloum, Mohammed

#### MRC Harwell, UK

Brown, Steve  
Mallon, Ann-Marie  
Weaver, Tom

#### Welcome Trust Sanger Institute, UK

Ramirez-Solis, Ramiro  
White, Jacqueline

#### Toronto Centre for Phenogenomics, Canada

Flenniken, Ann  
Nutter, Lauryl

#### Universitat Autònoma de Barcelona, Spain

Bosch, Fatima  
Ruberte, Jesus

#### CNR Monterotondo, Italy

Doe, Brendan  
Tocchini-Valentini, Glauco

#### Institute of Molecular Genetics, Czech Republic

Danek, Libor  
Sedlacek, Radislav

#### European Bioinformatics Institute, EMBL<sup>1</sup>

Koscielny, Gautier  
Meehan, Terry

#### BSRC 'Alexander Fleming', Greece

Kollias, George  
Kontoyiannis, Dimitris

#### Centre d'Immunologie, Marseille, France

Malissen, Marie

#### Helmholtz Zentrum for Infection Research, Germany

Kollmus, Heike  
Schughart, Klaus

#### University of Leuven, Belgium

Huylebroeck, Danny

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<sup>1</sup> Paul Flicek sent his apologies, he had to cancel his participation on short notice for private reasons



## 2 - International Steering Committee

The International Steering Committee is composed of those IMPC partners that are not direct partners of the InfraCoMP project.

### Australian Phenomics Network

Bertram, Edward  
Winslade, Stephen

### Charles River, USA

Elder, Bruce  
Morse, Iva

### Children's Hospital Oakland Research Institute, USA

West, David

### International Mouse Phenotyping Consortium

Moore, Mark

### Korea Research Institute of Bioscience and Biotechnology

Kim, Hyoung-Chin

### Model Animal Research Center, Nanjing University, China

Lei, Xiaojun

### National Institutes of Health, USA

Fletcher, Colin  
Peterson, Jane

### RIKEN BioResource Center, Japan

Masuya, Hiroshi  
Wakana, Shigeharu

### Seoul National University, Korea

Seong, Je Kyung

### The Jackson Laboratory, USA

Murray, Steve  
Svenson, Karen

### University of California Davis, USA

Golub, Mari  
Lloyd, Kent

## 3 – Additional Infrafrontier-IMPC Working Group Participants

Participants of the Common Infrafrontier-IMPC Working Groups not listed under 1 or 2

### Helmholtz Zentrum München, Germany

Aguilar, Antonio  
Becker, Lore  
Fessele, Sabine  
Hoelter-Koch, Sabine  
Janik, Dirk  
Lengger, Christoph  
Neff, Frauke  
Rathkolb, Birgit  
Rozman, Jan

### ICS – Mouse Clinical Institute, France

Birling, Marie-Christine

### MRC Harwell, UK

Blake, Andrew  
Cater, Heather  
Fray, Martin  
Greenaway, Simon  
Hough, Tertius

### MRC Harwell, UK (continued)

Morgan, Hugh  
Quwailid, Mohamed  
Teboul, Lydia  
Walling, Alison  
Wells, Sara

### Riken BioResource Center, Japan

Tanaka, Nobuhiko

### The Jackson Laboratory, USA

Chesler, Elissa  
Denegre, James

### University of California, Davis

Araiza, Renee

### Wellcome Trust Sanger Institute, UK

Adams, David  
Ryder, Edward

## 4 - Guests

### European Commission

Sambain, Brigitte

### The Jackson Laboratory, USA

Eppig, Janan



## II. Agenda

<b>Day 1</b>	<b>14 November</b>
12:00 – 13:00	<i>Lunch</i>
13:00 – 13:10	<b>Welcome</b> Martin Hrabé de Angelis
13:10 – 13:35	<b>Infrafrontier – Current Status</b> Martin Hrabé de Angelis
13:35 – 13:50	<b>The International Mouse Phenotyping Consortium – Current Status</b> Steve Brown
13:50 – 14:00	<b>Material Transfer Agreements and Industry</b> Mark Moore
14:00 – 14:25	<b>InfraCoMP – Providing a coordination mechanism between Infrafrontier and the IMPC</b> Michael Raess
14:25 – 14:40	<b>WP3 – Mouse Phenotyping (Topic 1)</b> Yann Herault – WP3 Lead
14:40 – 14:55	<b>WP4 – Mouse Production, Cryopreservation and Distribution (Topic 2)</b> Steve Brown – WP4 Lead
14:55 – 15:10	<b>WP5 – Access to Phenotyping Data (Topic 3)</b> Paul Flicek – WP5 Lead (presented by Michael Raess)
15:10 – 15:25	<b>WP6 – Community Engagement (Topic 4)</b> Ramiro Ramirez-Solis – WP6 Lead
15:25 – 15:40	<b>WP2 – Coordinating Infrafrontier and the IMPC</b> Michael Raess – WP2 Lead
15:40 – 16:00	<i>Coffee Break</i>
16:00 – 16:30	<b>General Discussion: Definition of tasks and how to proceed</b> Introduction by Martin Hrabé de Angelis
16:30 – 18:30	<b>Topic 2 - Mouse Production, Cryopreservation and Distribution</b> Chair: Steve Brown ES Cell Provision to IMPC – Access and Capacity <ul style="list-style-type: none"> <li>• KOMP Repository                      Kent Lloyd</li> <li>• EuMMCR                                      Wolfgang Wurst</li> <li>• Discussion</li> </ul> Cre Updates – Data and Recommended Lines <ul style="list-style-type: none"> <li>• Short presentations (5 mins) by representatives from Sanger, TCP, ICS, MRC Harwell, CHORI, JAX, HMGU</li> <li>• Discussion</li> </ul>
18:30 – 18:50	<b>Research Infrastructures in the next EU Framework Program (Horizon 2020)</b> Brigitte Sambain
20:00	<i>Conference Dinner (in the Hotel)</i>



<b>Day 2</b>	<b>15 November</b>			
08:30 – 08:40	<b>Topic 1 – Mouse Phenotyping</b> Introduction to the Common Working Group Yann Hérault			
08:40 – 10:00	<b>Common Infrafrontier and IMPC Working Group – Mouse Phenotyping</b> Chair: Yann Hérault Phenotyping Pipeline, SOPs, Timeline of Tests Three Breakout Sessions:  <table style="width: 100%; border: none;"> <tr> <td style="vertical-align: top; width: 33%;"> <b>Group 1:</b> <ul style="list-style-type: none"> <li>• B (Fertility and Viability)</li> <li>• C (SHIRPA, Dysmorphology)</li> <li>• D (Open Field)</li> <li>• E (Grip Strength; Acoustic Startle)</li> </ul> </td> <td style="vertical-align: top; width: 33%;"> <b>Group 2:</b> <ul style="list-style-type: none"> <li>• F (Echo/ECG)</li> <li>• G (Calorimetry/IPGTT)</li> <li>• H (ABR)</li> <li>• I (Body composition/X-ray)</li> <li>• J (Slit Lamp and Ophthalmoscope)</li> </ul> </td> <td style="vertical-align: top; width: 33%;"> <b>Group 3:</b> <ul style="list-style-type: none"> <li>• A (lacZ analysis)</li> <li>• K (Haematology; Clin Chem; Insulin)</li> <li>• L (Heart weight; gross pathology; block banking)</li> </ul> </td> </tr> </table>	<b>Group 1:</b> <ul style="list-style-type: none"> <li>• B (Fertility and Viability)</li> <li>• C (SHIRPA, Dysmorphology)</li> <li>• D (Open Field)</li> <li>• E (Grip Strength; Acoustic Startle)</li> </ul>	<b>Group 2:</b> <ul style="list-style-type: none"> <li>• F (Echo/ECG)</li> <li>• G (Calorimetry/IPGTT)</li> <li>• H (ABR)</li> <li>• I (Body composition/X-ray)</li> <li>• J (Slit Lamp and Ophthalmoscope)</li> </ul>	<b>Group 3:</b> <ul style="list-style-type: none"> <li>• A (lacZ analysis)</li> <li>• K (Haematology; Clin Chem; Insulin)</li> <li>• L (Heart weight; gross pathology; block banking)</li> </ul>
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10:00 – 10:15	<i>Coffee Break</i>			
10:15 – 12:00	<b>Common Infrafrontier and IMPC Working Group – Mouse Phenotyping</b> Chair: Yann Hérault Rapporteurs' summary of the Breakout Sessions Plenary Discussion on Phenotyping Pipeline and SOPs			
12:00 – 13:00	<b>IMPC Phenotyping Pipeline</b> Timeline Discussions and Resolution Yann Hérault and Steve Brown			
13:00 – 14:00	<i>Lunch Break</i>			
14:00 – 16:00	<b>Controls</b> Chair: Mark Moore <ul style="list-style-type: none"> <li>• Short reports (5 minutes) on handling of controls in different phenotyping centres: MRC Harwell (&amp; EuroPhenome), Sanger, KOMP 312 (CHORI), JAX, Japanese Mouse Clinic, ICS, GMC</li> <li>• Plenary Discussions on Controls</li> </ul>			
16:00 – 16:30	<b>Wrap-up</b> Martin Hrabé de Angelis			



### III. Discussions and Decisions

#### Setting the context for InfraCoMP

- In his **introduction to Infrafrontier** the coordinator of the programme, **Martin Hrabé de Angelis**, pointed out that Infrafrontier is a pan-European effort to **build a sustainable research infrastructure** for systemic phenotyping, archiving and distribution of mouse models. Meanwhile **a total amount of 135 Mio €** have been committed to the construction, upgrade and operation of national research infrastructure in the context of Infrafrontier. The Infrafrontier partners have **long-standing expertise** in cross-laboratory high-throughput systemic phenotyping, archiving and distribution. Infrafrontier is deeply rooted in the **ESFRI process** and the EC programs of **EUMORPHIA, EUMODIC and EMMA**. Infrafrontier provides trans-national access for individual research projects (**bottom-up**) and for large-scale programs (**top-down**). **InfraCoMP** brings together the Infrafrontier partners and the IMPC on a regular basis to discuss common strategies and solutions.
- The chair of the Steering Committee of the **International Mouse Phenotyping Consortium (IMPC)**, **Steve Brown**, presented the future vision of the project, to build an **encyclopaedia of mammalian gene function**. To this end, the IMPC will undertake **broad-based primary phenotyping of 20.000 mutants** of the IKMC resource (5.000 lines in Phase 1 from 2011 – 2016; 15.000 lines in Phase 2 from 2016 – 2021). The data will be freely available through the **Data Coordination Centre (DCC)**. The **IMPC phenotyping pipeline** has been defined in previous meetings and a series of conference calls, its fine-tuning is an aim of the current meeting. **Future challenges** for the IMPC are addressing of aging phenotypes, setting-up an effective data acquisition, data analysis and data dissemination pipeline, developing approaches to describe and map phenotypes to human disease states, the general networking with the community, and the integration with the phenotyping of other genetic reference populations.
- The executive director of the IMPC, **Mark Moore**, related to the issue of **material transfer agreements (MTAs)** and industry. Currently, there is **no standardised MTA available** across IMPC partners. **Known issues** are the long periods it takes to process the MTAs, the requirement for re-visiting the same issues all over on new requests, distinguishing between 'commercial purposes' and 'for-profit entities', and the transfer of materials to third parties. An MTA for IMPC purposes should ideally be standardised across all partners and **allow rapid transfer** of mice and materials across IMPC members, to IMPC collaborators and to third parties.
- The project manager of **InfraCoMP**, **Michael Raess**, explained that the project will deliver **a series of dedicated workshops and reports** to develop **common strategies and approaches** of Infrafrontier and the IMPC relating to the following topics: **Topic 1** – Mouse phenotyping; **Topic 2** – Mouse production, cryopreservation and distribution; **Topic 3** – Access to phenotyping data; and **Topic 4** – Community engagement. These topics are reflected in InfraCoMP's **thematic work packages**. InfraCoMP will organise a series of six common **workshops** (including the current meeting) in the course of the next three years (the project runs until September 2014). The workshop agendas will be set by the **coordination work package** with input of the **International Steering Committee** (non-Infrafrontier IMPC members) and of the thematic work packages. Each workshop will result in a **meeting report** that will be made available to the public via the Infrafrontier website (in a dedicated InfraCoMP section).
- The **InfraCoMP work package leaders** gave short overviews on the main objectives, tasks, and deliverables in their work packages: **Yann Hérault** for WP2 – Mouse phenotyping; **Steve Brown** for WP3 – Mouse production, cryopreservation and distribution; **Michael Raess** (substituting **Paul Flicek**) for WP5 – Access to phenotyping data; and **Ramiro Ramirez-Solis** for WP6 – Community engagement.
- **Brigitte Sambain** from the **European Commission** gave an outlook to the upcoming **International Conference for Research Infrastructures (ICRI 2012)** and provided details on the planned activities for research infrastructures in the upcoming framework programme for research and innovation – **Horizon 2020**. The research infrastructures programme will be part of the 'Excellent Science' pillar of Horizon 2020, together with the ERC, the Marie Curie actions and the Future and Emerging Technologies programme. **Main actions** will be the developing of new world-class research infrastructures, which includes support for the **implementation and operation for ESFRI projects** such as Infrafrontier. The support of the integration



of national research infrastructures (current I3 instrument) will continue. Among the policy actions will be the **facilitation of strategic international cooperation** of European research infrastructures.

## WP3: Mouse production, cryopreservation and distribution

Chair: **Steve Brown**

- KOMP Repository as well as EUMMCR will face **increased demands** to provide the ES cells for IMPC Phase 1. Both, **Kent Lloyd** as well as **Wolfgang Wurst** state to have **sufficient capacities** in their facilities to serve the IMPC as well as the wider community.
- ES cell delivery times will have impact on **IMPC gene selection scheme**; re-assessment may be required later on.
- The gene selection process will be supported by the **iMits database** which started successfully in October. It is still an evolving system and certain issues need to be revisited together with Vivek.
- Most of the centres presented **successful approaches for neo removal**. They are also willing to **share** their Cre deleter lines and strategies with other centres. Overall the **IMPC will not be prescriptive** which strategy to use.
- The optimal way for **cryo-preservation** would be to freeze the tm1a as well as the tm1b allele (taking into account the relatively low costs of sperm freezing). In case of financial restrictions the tm1a allele should be preserved.

## WP2: Mouse phenotyping – Common phenotyping working group

Chair: **Yann Herault**

In three breakout sessions the respective tests and **SOPs** were discussed by the specialists and the results reported back to the plenary session for final discussion.

### Group 1:

- **Viability:** Agreement on test scheme, viability will be called after 28 pups: no homocygotes → call is lethal; <13% homocygotes → call is subviable)
- **Fertility:** Mandatory test, minimum requirements for infertility and data reports fixed: minimum of 2 homs of each sex mated to non-hom animals; no. of pups recorded.
- **Open Field:** non-mandatory; Standard SOPs based on EUMODIC
- **SHIRPA/Dysmorphology:** These two tests are now fused; parameters and scoring systems to be finalised.
- **Grip Strength:** Will employ the Helmholtz custom-made grid.
- **Acoustic Startle / Prep-Pulse Inhibition:** SOP under refinement

### Group 2:

- **Echo/ECG:** not all centres can apply ECHO, SOPs to be developed; non-mandatory
- **Calorimetry:** Different test durations will be allowed (reflected in SOPs); centres should stick to one scheme
- **Fasting:** overnight
- **ABR:** Undertaken jointly with X-ray and DEXA
- **X-ray:** Number of projections to be agreed upon on
- **DEXA:** qNMR as alternative
- **Slit Lamp / Ophthalmoscope:** OCT and Scheimpflug as optional technologies

### Group 3:

- **Blood collection:** Agreement on standardised procedure by retro-orbital bleeding
- **Hematology:** Follow EUMODIC SOP
- **Clinical Chemistry:** Minimum test panel to be identified



- **Immunology:** Flow cytometry of blood is the standard. Spleen FACS will be assessed in a high-throughput setting but a uniform test for the IMPC would be desired. Ig measurements optional for naive animals.
- **LacZ:** non-mandatory: 3 protocols but no prescription of technical details. There has been discussion on both adult and embryo lacZ expression studies, but a minimum consensus approach has yet to be finalised. We need to establish a cross-centre working group to develop a coherent IMPC strategy, and a minimum consensus plan that can be utilised to estimate costs
- **Heart Weight, Gross pathology, Block Banking:** An agreed minimum SOP and Tissue Collection Survey to be completed. Sectioning and H&E optional

## WP2: Mouse phenotyping – IMPC phenotyping pipeline: Timeline discussions and resolution

Chairs: **Yann Herval** and **Steve Brown**

### General points

- Phenotyping tests run from in-life platforms starting at 9 weeks to terminal tests at 16 weeks
- Weights are measured weekly from 4 to 16 weeks
- Cohorts of 7+7, unless otherwise stipulated

### Agreed on changes:

- Dymorphology/SHIRPA fused together
- ECG/ECHO: test status changed to test in development
- DEXA for body composition
- X-ray moved to week 14
- Pain Test out
- FACS analysis: blood (spleen will be tested in a high-throughput setting)

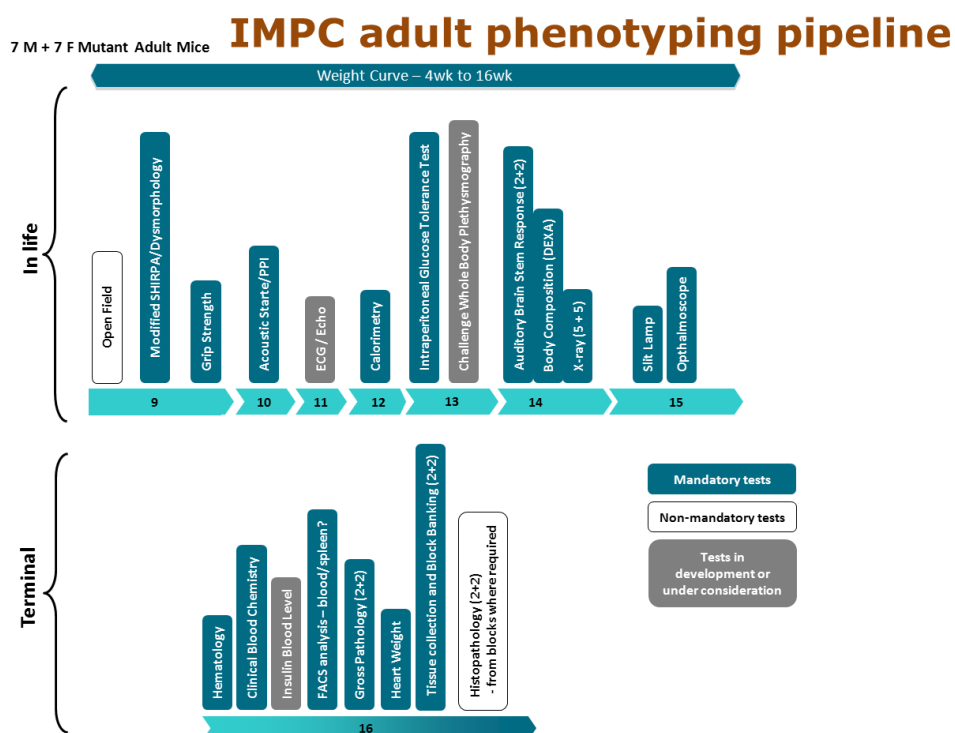


Fig. 1: Proposed IMPC adult phenotyping pipeline



## Controls

Chair: **Mark Moore**

**Short reports** on handling of controls in different phenotyping centres:

- **MRC Harwell:** litter mates / B6N tac baseline controls
- **WTSI:** KOxKO colony control weekly/historical
- **KOMP312:** WT litter mates (15%) historical
- **JAX:** KOxKO colony control 5/week; 3 week window, population extraction
- **JMC:** B6N tac internal vs external; 7+7 monthly
- **ICS:** WT litter mates / B6N tac baseline controls
- **GMC:** litter mates / B6N tac baseline controls

**Minimum recommendation:** B6N colony bred controls providing cohort as well as global baseline controls (ratio WT:KO to be decided)

Population controls AND x week window

**Littermates:** Some centres will trial littermates for comparison

Centres will apply different control schemes but they must be scientifically and statistically valid.

A Statistics Working Group should be established to undertake discussions on the appropriate statistical analyses of control data.

## IV. Next Steps

### Action points:

- **Gene Selection**
  - ES cell delivery times will have impact on **IMPC gene selection scheme**; re-assessment may be required later on.
- **Phenotyping pipeline / SOPs**
  - **SHIRPA/Dysmorphology:** Scoring systems need to be finalised.
  - **Acoustic Startle / Prep-Pulse Inhibition:** SOPs need refinement.
  - **Echo/ECG:** development of SOP required.
  - **Calorimetry:** Different test durations will be allowed this has to be reflected in SOPs.
  - **X-ray:** Number of projections need to be agreed upon on.
  - **Clinical Chemistry:** Minimum test panel needs to be identified.
  - **Immunology:** Spleen FACS needs to be assessed in a high-throughput setting.
  - **LacZ:** A minimum consensus approach for adult and embryo lacZ expression studies has to be finalised. A **cross-centre working group** should be established to develop a coherent IMPC strategy, and a minimum consensus plan that can be utilised to estimate costs.
  - **Heart Weight, Gross pathology, Block Banking:** An agreed minimum SOP and Tissue Collection Survey has to be completed.
- **Controls**
  - A **Statistics Working Group** should be established to undertake discussions on the appropriate statistical analyses of control data.

### Next InfraCoMP Meetings

- **Spring meeting**
  - London, around April 17
  - Developmental pipeline
  - Update and finalisation of IMPC phenotyping pipeline
- **Fall meeting**
  - November, probably outside Europe (Washington DC? Toronto?)