InfraCoMP Workshop on IMPC Embryonic Lethal Screening

WednesdayApril 18th- Thursday April 19th, 2012

Institute of Child Health, University College, London, UK

Venue

Kennedy Lecture Theatre, Institute of Child Health, University College London, London NW1 2BE, UK. Tel: +44 (0)20 7611 8888.

Meeting Information & Logistics:

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Organizers:

Chair, Janet Rossant, University of Toronto, Canada
Andy Copp, ICH/UCL, London, UK
Tom Weaver, MRC Harwell, Oxford, UK
Tim Mohun, MRC, NIMR, London, UK
Monica Justice, Baylor College of Medicine, Houston, USA
Martin Hrabé de Angelis, HMGU, Munich, Germany
Michael Raess, HMGU, Munich, Germany

Background

The International Mouse Phenotyping Consortium (IMPC, www.mousephenotype.org) was launched in September 2011 with the initialgoal to create 5,000 targeted knockout mouse strains (C57BL/6N) over the next five years. If successful, the program will be scaled to eventually complete the genome (20,000 genes) by 2021. Strains will be cryopreserved and then expanded so that cohorts of adults can undergo a suite of phenotypic tests. All strains will be accessible through public biorepositories and phenotypic data will be immediately released and available through a central public database. The first global project meeting, called "InfraCoMP – Coordinating the cooperation of Infrafrontier and the IMPC", (www.infrafrontier.eu/infracomp.php) was held recently in Munich (Nov, 2011) and the screening pipelinewas agreed by participating partners (www.mousephenotype.org/workgroups/impc-phenotyping-work-group). Included in this set of tests is a measure of homozygous lethality before two weeks of age, as well as an optional analysis of LacZreporter gene expression at embryonic stage E12.5. This superficial level of phenotyping however will miss a treasure trove ofvital information generated by gene loss during embryonic development where we expect 30-40% of all knockouts to be lethal.It is timely therefore to consider how the IMPC can exploit its unique position and resources to **INCORPORATE A DEDICATED EMBRYONIC LETHAL SCREENING PIPELINE**in order to:

- **Provide insight into the underlying developmental causes and timing of lethality**, identifying disruptions in cellular, tissue and organ systems using 3-D imaging and possibly other molecular or cellular techniques;
- **Deepen our understanding of gene functionand pleiotropy during development**, identifying embryonic acting genes/pathways that arecritical for multiple tissues and developmental stages;
- **Help interpret adult phenotypes,** leading to better models of human disease;

- **Respond to the needs of the research community**, where two large surveys of experts, including both developmental biologists and clinical researchers, as well as dedicated workshops (Toronto, April 2010; Barcelona, Feb 2011) have overwhelmingly recommended that focusing on embryonic lethality should be of the highest priority for the IMPC;
- **Deliver much more useful data at relatively minimal additional effort and cost**, since cohorts for the adult pipeline can be used to generate embryos;
- **Exploit a unique and possibly one-off opportunity** to carry out such a screen in mice.

Objective of the Workshop

Our task in this workshop is to consider the scientific, operational, IT and other resource requirements for a screen and **agree aconsensus strategy for embryonic phenotyping**to recommend to the IMPC steering committee for implementation across the consortium by as many partners as possible.

Key elements of this strategy should include:

- **Scientific Value of Embryology to Research Community:**What is the real value of the proposed pipeline to the community? Should single or multiple stages be analyzed? Should all strains be tested at all stages/platforms or some triaged to specialist labs? Should we identify target communities with which to partner (eg GWAS programs, consortia)? If so, what mechanisms can be put in place to directly link IMPC embryonic phenotyping effort with these programs? Can we engage with expert users in the community to help with annotation? If so, how is this best approached (is there precedence from other programs)?
- **Current Status of Screening:**Do similar KO mouse embryonic phenotyping programs exist or are they being planned? If so, how can we synergize with their efforts? Are there programs in other model organisms that can advise our efforts (eg data capture/annotation)?Do participating centres/funders have funding streams we can tap into, or would the funds have to come from existing budgets? Important output = What time point(s) should be screened to provide max value?
- **Operational Workflow:**What platforms can be employed to study embryonic lethals? Can a mixture of platforms be used? What can be realistically bootstrapped to the IMPC (breeding capacity, access to specific platforms)? What key resources are required (capital, technical support and development, animal numbers, specialist reagents)? What is the ballpark cost for performing such a screen? Can a distributive model work (eg centralized imaging centres, possibly focusing on different modalities).
- **LacZ Reporter Analysis:**This platform was left unresolved at the last IMPC/InfraComp meeting in Munich and a common way forward needs to be agreed. What is the best strategy for characterizing LacZ reporter activity? What is the impact of some centres not carrying out LacZ analysis?Can the current plan to carry out limited LacZ analysis of embryos be combined/replaced with an embryonic phenotyping study (eg OPT)? Is LacZ imaging the only route forward, or do other molecular methods such as RNAseq have a role in the screen?
- **Information Technology:**Identify issues for production centers and the DCC in terms of data capture, storage, analysis and annotation.Are there exemplar programs that exist now, can these be adapted for our purposes? How can we use anatomy “atlases” for automated phenotyping, image presentation & annotation? Can annotation systems be employed such that remote annotation is achievable, both within production centres and possibly expert external collaborators?

DRAFT AGENDA:

DAY ONE:

Session 1 Value of Embryonic Phenotyping – Janet Rossant, Chair

10:00 – 10:15 Intro, aims, work plan for the two days – Janet Rossant

10:20–10:40 Importance of embryonic phenotyping, what value to end user? – Andy Copp

10:40 – 11:00 Importance of embryonic phenotyping, ENU case study - Monica Justice

11:00 – 11:30 Discussion: What time point(s) should be screened to provide max value?

11:30 – 12:00 Coffee Break

Session 2 Imaging Modalities for Embryonic Screening, Monica Justice, Chair

12:00 – 15:00 TBD.

13:00-14:00 Lunch

Session 3 Screens in Development, Tom Weaver, Chair

15:00 – 15:20 TCP Screen in KOMP2/NORCOMM2 – Mark Henkelman, UnivToronto

15:20 – 15:40 PREMIM/Welcome Trust proposal for embryonic phenotyping - Tim Mohun, MRC NIMR

15:40 –16:00 General discussion: How much can we build upon these efforts &funding opportunities.

Session 4: Information Technology and Analysis, Richard Baldock, Chair

16:00 – 18:00 (1) Infrastructure (open source); (2) Annotation (what it is and how to represent it); (3) Mapping phenotypes, atlases; (4) Visualization and Community Access; (5) Analysis tools.

17:30 Close of First Day

19:00 Dinner Somewhere in London

Day Two:

Session 5 **LacZ Expression Profiling, Value and Strategy, David West, Chair**

8:30-10:00 Scientific case studies for large-scale screens. Combining LacZ with embryo phenotyping. Role of transcriptomics?

10:00 **Coffee Break**

Session 6: **Adult phenotyping pipelines and control**

10:30 – 11:00 Adult phenotyping pipelines and SOPs, Update from Munich. Steve Brown, Chair

Parallel Sessions:

11:00 – 13:00 Statistics working group: Strategy for controls. Elissa Chesler, Chair

11:00 – 13:00 Break out working groups: Useful for extending IT discussions.

13:00-14:00 **Lunch**

Session7: **Consolidate Recommendations and Actions, Janet Rossant, Chair**

14:00 – 16:00 Chairs of each session to present their summary recommendation (10' plus 10' for Group Discussion)

16:00 **Close of Second Day**