MRC Mouse Network: Research Consortia Expressions of Interest – FAQs

Questions and answers regarding the IMPC resource, application eligibility, preparing an expression of interest, and assessment.

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Information about the mouse knockout and phenotyping resources available

Q: What is the IMPC and how is it managed?

A: The International Mouse Phenotyping Consortium (IMPC) is composed of academic, charitable, and government research institutes and funding bodies (**www.mousephenotype.org**). Its purpose is to coordinate the creation of 20,000 targeted gene knockouts in mice, undertake a series of primary phenotypic tests, and facilitate access through centralized mouse distribution and data coordination centres. The IMPC is governed by a steering committee, composed of stakeholder organizations and a scientific chairman. The day-to-day co-ordination of the consortium activities is delivered by the IMPC Secretariat, under the leadership of the IMPC Executive Director.

Q: What is the MRC Mouse Network?

A: The MRC Mouse Network has been created in order to provide UK scientists with a forum to engage with the IMPC programme. All UK scientists are welcome to join the MRC Mouse Network where they will receive regular updates about access to:

(1) **MUTANT MICE:** a steadily growing collection of strains which are multifunctional in terms of their application to genetic research (e.g. null alleles, reporter gene expression, conditionality),

(2) **PHENOTYPIC DATA** from a variety of therapeutically relevant systems collected for each mutant strain (primary phenotyping data), and

(3) **COLLABORATIVE RESEARCH & TRAINING** opportunities between members of the network, building on their basic or clinical research in academia or industry.

Q: What is the MRC Call for "Expression of Interest" for Research Consortia and what are the benefits?

A: The purpose of the MRC Call for Expression of Interest (EoI) is to create within the MRC Mouse Network a number of "Research Consortia" which will shape the MRC's prioritisation of KO lines for phenotyping and engage with the IMPC programme through MRC Harwell (Mary

Lyon Centre and Mammalian Genetics Unit). Consortia will be selected on several criteria, including track record, ability to work with mouse models, and engagement with other labs, particularly those carrying out human genetics and clinical research. The benefits to a successful consortium include:

- Ability to nominate genes of your choice for creating conditional KO mouse lines and subsequent phenotyping
- Early information on the progress of establishing the KO colonies and phenotyping activities which will have direct bearing on their individual research programmes
- Influence on the primary phenotyping tests performed and how they are analyzed
- Access to the expertise within MRC Harwell and other mouse consortia
- Participating labs will also be encouraged to influence the scientific direction of the mouse program and apply for future research funding from the MRC or other agencies to support secondary phenotyping activities made possible through the IMPC.

Q: What is the IKMC and associated resources?

A: The International Knock-out Mouse Consortium (IKMC) has evolved over the last 10 years. It's origins came from a collective desire to exploit high-throughput mutagenesis technology (e.g. Zamrowicz et al. 1998, Nature 392, 608; Nolan et al. 2000, Nature Genet. 25, 440) to functionally annotate the mammalian genome, a vision first set out in a white paper in 2001 when the Human genome was completed (Nadeau et al. 2001, Science 291, 1251). A subsequent Banbury Conference (CSHL, USA) held in 2003 brought together many leading academic and commercial researchers to develop an operational roadmap which proposed a phased approach. The first phase aimed at systematically targeting or trapping every gene (20,000) in mouse ES cells to create a genome-wide collection of null alleles that also contain a lacZ reporter cassette. The next phase would involve creating mouse strains from the ES cell resource and perform "tiered" phenotyping, beginning with tissue expression analysis from the reporter, followed by broad based phenotyping and ultimately specialist detailed phenotyping. All resources (ES cells, mice and data) would be made freely available through public biorepositories and data coordination centres. This program became known as the Knock-Out Mouse Project, or "KOMP" (Austin et al. 2004, Nature Genet 36, 921) and was funded through a series of initiatives at the NIH, including: (1) the acquisition of 250 mouse knock-out lines and associated phenotypic data generated by the companies Deltagen and Lexicon Genetics; (2) a program of invited repatriation of published KO mice; and (3) producing and archiving for distribution 8,500 KO ES cell lines (3500 deletions, 5000 targeted conditional ready alleles) and 500 mutant mice made through centralized operational production centers at Regeneron, UC Davis, CHORI and the Sanger Institute. A similar roadmap was developed in the EU called the European Conditional Mouse Mutagenesis Program (EUCOMM), (Auwerx et al 2004, Nature Genet 36, 925), which was funded through an EU framework program to create 20,000 mutations (12,000 conditional gene trap and 8,000 conditional targeted alleles) as well converting 320 into mice. These two major initiatives were combined under the single IKMC (Collins 2007, Cell 128, 9) together with the TGEM Genetrap program (Texas, USA) creating 10,000 genetraps, and the North American Conditional Mouse Mutagenesis Project (NorCOMM) which is creating 10,000 gene traps and 2000 conditional targeted null alleles, and 100 mouse strains. Each of these programs is rapidly reaching their conclusion, having met their targets. Recent funding decisions have been announced to expand the program, including EUCOMM Tools which will create a further 3500 conditional targeted alleles in ES cells and a collection of 500 CRE-driver lines, 250 of which will be available as mice. The IMPC will be a further extension of this program, with initial funding from NIH, Wellcome Trust, MRC, and Genome Canada committed to deliver between 4000-5000 mutant mice and phenotypes from the IKMC resource.

Q: What IMPC resources will be available and are they conditional alleles?

A: The IMPC will make available to all researchers all mice and data as soon as each has passed the full quality control tests. We are planning to archive two different alleles, the first will be the "null first conditional ready" allele (Testa et al. 2004, Genesis 38, 151) called "TM1a" in our schematic *www.har.mrc.ac.uk/MRCMouseNetwork/EUCOMM_allele.pdf*. This is a null allele containing both the lacZ reporter and neo cassettes, and mice will be cryopreserved and available as sperm. Although these mice are NOT CONDITIONAL, they can be easily converted to a conditional allele by breeding with Flp-recombinase which removes the reporter and neo cassettes and reverts to wild-type expression but as a fully conditional null-allele (called "TM1c" in the schematic). The second allele available is called "TM1b" and is derived from the null first conditional ready allele TM1a by breeding with Cre-recombinase. TM1b allele has both critical exon and neo cassettes removed, this is important since the neo promoter is known to affect local gene activity and influence phenotypes. Mice carrying the TM1b allele will be undergo primary phenotyping and also will be archived as both sperm and embryos. Because Tm1b strains will be bred as large cohorts of mice for phenotyping they may be available as live mice depending on timing of request.

Q: What if a line cannot be produced?

A: The IMPC is working under high throughput conditions which means although there are many quality control and assurance steps in place to achieve the highest quality results, the operational systems are not 100% efficient. ES cell targeting, chimera production, germ-line transmission, fecundity and lethality will all vary between lines. The nature of high throughput operations means that it is more efficient to have a singe-pass attempt for each gene rather than repeat attempts of the same gene. This means that for any single gene that gets nominated to the pipeline there is approximately a 50% chance that it will make it through the full program. This point should be taken into account when nominating candidate gene lists.

Q: How will researchers access the resource?

A: Information on the progress of each MRC line will be communicated directly to Research Consortia through the MRC Mouse Network. A dedicated website has been created for the MRC Mouse Network, please see *www.mrcmousenetwork.org*. Once mouse lines and data have passed internal quality control checks they will be made available. On-line resources already exist at Harwell for mice (*www.mousebook.org*) and phenotyping data (*www.europhenome.org*). Additional portals will exist that will combine all the data from MRC and other IMPC centres, such as for mice (*www.knockoutmouse.org*) and phenotyping data (part of centralized data coordination centre yet to be established).

Q: Will I be able to influence the battery of tests?

A: The pipeline of tests used for IMPC is still being considered. A series of international workshops have been held over the last few years to work up a recommendation, taking into account the experiences from pilot large-scale efforts (e.g. EUMODIC). The most recent workshop in Barcelona (March 2011) compiled a draft report describing an optimal pipeline. This report can be accessed through the IMPC website (*www.mousephenotype.org*) and the MRC Mouse Network will be able to comment on the draft pipeline either directly to the IMPC working group or through communication with Dr Tom Weaver, Director of the MRC Mary Lyons Centre. It should be noted that the pipeline will most likely evolve over time and the MRC Mouse Network will be instrumental in influencing any decision as to how to improve the pipeline.

Q: How long will it take to access data on a gene that has been nominated?

A: The time it takes to make a mouse (germ line transmission) to cohort generation, archiving and phenotyping is in the order of 18 months. The overall timeframe for producing mouse lines is five years. The capacity for production dedicated to this call will be about 60 lines per year. Thus the time frame for delivery of a particular line will be dependent on its place in the queue. Note that it can take up to 12 months to complete all the operational procedures and quality control testing before a line will be available. A list of genes selected and underway will be available and all Research Consortia will be kept informed of the progress of their chosen lines.

Eligibility

Q: Who is eligible?

A: The lead applicant must be a UK based researcher (although collaborators on the application can be international), or at an overseas establishment supported by any of the Research Councils.

Q: Can Research Council establishments (units and institutes) apply under this call?

A: Yes.

Q: Is my UK institution eligible?

A: Eligible organisations fall into three categories:

- UK Higher Education Institutions (HEIs);
- Research Council institutes;
- Independent Research Organisation (IROs).

Please see eligibility for Research Council funding for further details.

Q: Is there a limit to the number of Expressions of Interest I can submit?

A: Following projections of likely interest, an eligible individual may submit a maximum of either (i) one Expression of Interest as a PI and one as a co-applicant, or (ii) two Expressions of Interest as a co-applicant. An individual may be a collaborator on any number of Expressions of Interest in addition to the above.

Q: Are there specific partnerships that are expected?

A: Expressions of Interest including partners from the UK murine pathophysiology, human genetics, and/or medical communities are expected.

Funding

Q Is any funding awarded under this call?

A: No funding is to be awarded under this call for Expressions of Interest. The aim of the call is to identify Research Consortia to prioritize the production and high throughput phenotyping of 250 gene knock-out mice by MRC Mary Lyon Centre as part of MRC's partnership in IMPC. Research Consortia will also be invited to participate in the MRC Mouse Network. The purpose of the MRC Mouse Network is to ensure that the MRC IMPC programme fully engages with the

UK research community, and help ensure that MRC's investment into the IMPC initiative is being fully utilized by the UK research community and propagated into follow-on blue skies or translational research programmes.

Preparing an application

Q: How do I submit an Expression of Interest?

A: Expressions of Interest should be submitted as a PDF via email to: *MRCeventsandcommitteesteam@headoffice.mrc.ac.uk*

Applicants should refer to the Expression of Interest guidance notes for further information.

Q: When is the deadline for submission of Expressions of Interest?

A: 4pm, **Wednesday 31st August 2011**.

Q: When will applicants be notified of decisions?

A: Applicants will be notified of decisions in early **October 2011**.

Q: What happens after decisions have been made?

A: Successful applicants will be also contacted by Dr Tom Weaver, Director of the MRC Mary Lyons Centre to discuss participation in the MRC Mouse Network.

Q: Is there a restriction on the typeface/pitch for the Expression of Interest?

A: Yes, applicants must use Verdana 10 point typeface for the content; which is the standard typeface on all MRC applications.

Q: What is the page limit for the scientific case?

A: Six pages, including references and all the sections described in the guidance and evaluation notes for the Expressions of Interest.

Q: Can I create my own scientific case document?

A: Yes, provided that you address the specific headings listed in the guidance as these will be used to assess your application. Please refer to guidance and evaluation notes for Expressions of Interest for information.

Q: Can I include annexes in my application?

A: Only include CVs of each of the Principal Investigator and Co-Investigators combined in a single annex.

Q: What happens if my Expression of Interest is received after the deadline?

A: Any Expression of Interest received after the deadline will not be considered.

Assessment

Q: What is the assessment process?

A: There are no external referees involved in assessing the Expressions of Interest. Assessment will be made by a MRC Cross-Board Advisory Group.

Communications

Q: How will you let me know if my Expression of Interest has been successful?

A: We will notify the Principal Investigator of the decision by email communication.

Q: When can I expect to receive feedback on whether my Expression of Interest has been successful?

A: Notification of the outcome will be made by **mid October 2011.**

Q: If my query is not answered by the FAQ's, or by the specific guidance in the Expressions of Interest notes, how do I contact you?

A: For administrative queries relating to this Call, or for scientific queries about the submission of an Expression of Interest (e.g. MRC strategy in this area, the contents of the case for support/proforma), please contact: *MRCeventsandcommitteesteam@headoffice.mrc.ac.uk*.

A: If you have scientific and technical questions about the IMPC, the MRC IMPC resources available, gene prioritisation, generation of mouse knockouts, phenotyping, the MRC Mary Lyons Centre, etc., please contact:

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