Call 2016: 'Mouse models and rare diseases'

The French Foundation for rare diseases (Fondation maladies rares) and the French National Infrastructure PHENOMIN, which includes the Institut Clinique de la Souris (ICS, Illkirch), the Centre for Immunophenomics (CIPHE, Marseille) and the Transgenesis and Archiving of Animal Models (TAAM, Orléans, Villejuif) are pleased to launch their 3rd joint call for the creation and exploration of mouse models for rare diseases.

Submission deadline for proposals: January 31, 2017, 5:00 pm

A – Context and aims of the call

The call for projects **'Mouse models and rare diseases'** aims to give a significant boost to the development of mouse models, in order to:

- gain **a better understanding of the pathophysiological mechanisms involved in rare diseases** whose defective genes have been identified;
- **test and validate therapeutic proofs of concept**, at the pre-clinical *in vivo* level.

Indeed, producing these models meets **a key objective in the development of a therapeutic strategy**. After their initial *in vitro* testing, therapeutic proofs of concept must be tested in a living model that recapitulates as closely as possible both the phenotype and biological defects associated to the human disease. Such a model should provide appropriate data regarding the safety and the efficiency of the drug, thus evaluating its benefit/risk ratio, prior to conducting early phases of a therapeutic trial.

PHENOMIN and the French Foundation for rare diseases combine their efforts in order to achieve these objectives through the joint call for proposals for the **generation and characterization of mouse models, dedicated to rare diseases**.
This action is part of the objectives of PHENOMIN to develop **mouse model resources** that will be made available to the scientific community.

B – Content of the call for proposals (see the summary diagram in Appendix)

This call for proposals is open to research projects covering **all rare diseases.**

For rare cancers, the French National Cancer Institute, INCa, and the French Foundation for rare diseases have defined jointly the following criteria:

- projects concerning primary malignant tumors should be addressed to INCa,
- projects concerning benign tumors as well as systemic rare diseases involving tumor development will be evaluated within this call.

The principal investigator of the project must belong to a French research team**,** affiliated to academia (research team working in universities, other higher education institutions or research institutes) and/or to clinical/public health sector (research team working in state or university hospitals/public health organizations).

The aim of the call is in compliance with the goals set by the International Rare Diseases Research Consortium (IRDiRC).

One distinct submission form must be filled per independent mouse model.

The call is dedicated to generating mouse models. Standard phenotyping can be proposed on the generated mutants. Any other request (breeding, specific phenotyping …) is not eligible.

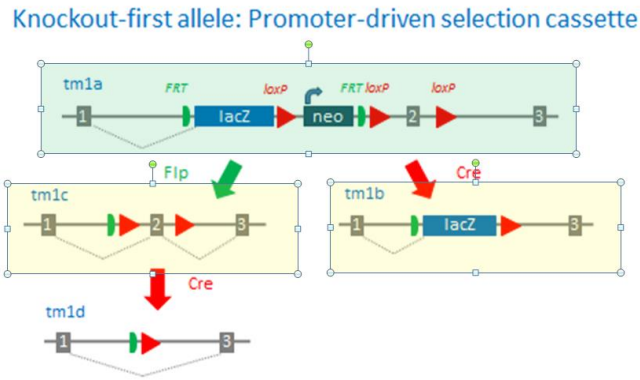
1- Generation of mouse models

a. Knock-Out constitutive, conditional mice:

Knock-Out models will be generated either:

1) from ES cells derived from the international IMPC resource (www.knockoutmouse.org). Models will be generated on a C57BL/6N genetic background. Knock-Out models with conditional potential (KO-first allele, tm1a) will be first produced; Knock-out by disruption of a critical exon (knock-out tm1b allele) and Conditional Knock-Outs (cKO tm1c allele) can then be provided by using Cre/LoxP and Flp/FRT systems.

KO-first allele, tm1a is provided, tm1c or tm1b alleles are provided on request:



2) In case of ES clones unavailability from the IMPC resource,

- **constitutive Knock-Out** models will be generated by the CRISPR/Cas9 nuclease technology (C57BL/6N genetic background only),
- **conditional Knock-Out** models will be generated *de novo* by ES-based methods (C57BL/6N genetic background only)).

b. Knock-In mice:

Knock-In mice [reporter gene, point mutation, humanization, targeted transgenesis (ROSA26), but excluding complex modifications] will be generated *de novo* by the PHENOMIN infrastructure in C57BL/6N genetic background.

c. Transgenic mice:

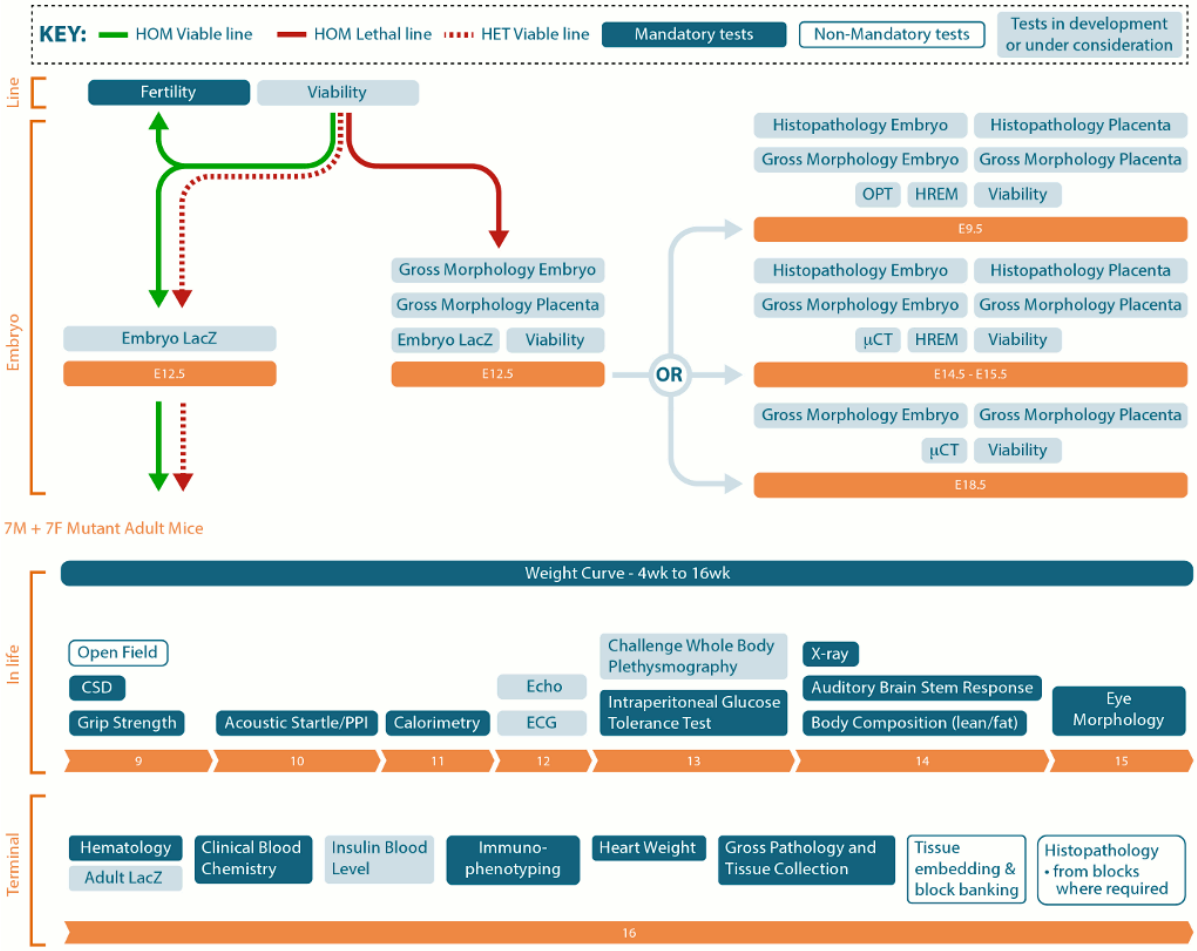
Transgenic mice (overexpression by pronuclear injection in C57BL/6N fertilized oocytes, but excluding complex constructs) will be generated *de novo* by the PHENOMIN infrastructure.

2- Expansion and phenotyping

All Knock-Out models (with conditional potential) derived from the IMPC resource and KO generated by CRISPR/Cas9 will be phenotyped according to a standard scheme defined by the members of the international consortium IMPC (www.mousephenotype.org).

Models generated *de novo* by the PHENOMIN infrastructure can be phenotyped according to the same scheme, at the request of the principal investigator and after assessment of the application - the added value to achieve a global standard phenotype will be evaluated.

IMPReSS standard phenotyping scheme



3- Models generation, phenotyping and data availability to the investigator and to the scientific community

Models generated from the IMPC resource will be sent to the principal investigator of the project within 8 to 16 months after obtaining necessary information and materials to start the project. The majority of projects are completed within 12 months following the initiation of the project. More time may be necessary in a few cases, depending on the time needed to obtain the IMPC clones or to achieve the targeting constructs.

Models generated *de novo* will be provided to the principal investigator within an average of 18 months (minimum period: 12 months).

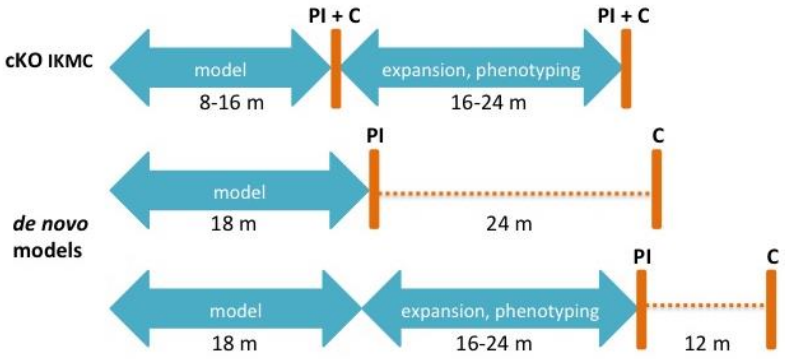
The progress of each project will be monitored and updated every 6 months by the PHENOMIN project manager and communicated to the principal investigator.

Phenotypic data will be available within 16 to 24 months after delivery of the model to the principal investigator.

According to the IMPC consortium rules, **Knock-Out first models (with conditional potential) generated from this resource** and **knock-out models generated by CRISPR/Cas9 genome editing technology** will be made available to the principal investigator of the project and to any interested group, as soon as germline transmission is confirmed. Similarly, phenotypic data will be made available to the scientific community through a single database accessible on the web. The IMPC program provides a single web-based database referencing all resources. Any model already completed or underway in the world is thus made available to any interested group almost in real time.

Models generated *de novo* by the PHENOMIN infrastructure will be provided first to the principal investigator. Models will be preserved and archived and will then be made available to the whole scientific community within 24 months. The IMPC standard phenotypic data will be made available to the community within 12 months.

Diagram of time provision of models and phenotypic data



PI: principal investigator **C : community**

C – Technical eligibility check

Technical eligibility of the project must be checked and approved by the platform before submission. The PI must contact PHENOMIN using contact@phenomin.fr for submitting the scientific context of the project (20 lines maximum) stating in the email subject "Call 2016: Mouse models for rare diseases". A precise scientific question must be addressed in order to be able to define the best model generation approach. The MGI reference gene must be stated. A conference call can be scheduled in order to address the feasibility and define the most suited design for the project. **This procedure is mandatory and should be planned early in the process in order to ensure timely submission of the project.**

1. **Knock-Out constitutive, conditional models:**

Several cases are possible.

- *Case 1: The model is already available or is developed by another IMPC resource center.*
  In this case, the proposal is not eligible. The principal investigator will be informed of the corresponding center.

- *Case 2: Three ES mutant clones with conditional inactivation of the gene are available.*
  These clones are referred to as "clones with conditional potential" on the IMPC website (www.knockoutmouse.org).
  In this case, only the recombinant ES clones generated by the consortium IMPC will be used for successful applications.

- *Case 3: For projects that do not match any of the two afore mentioned cases.*
  The *de novo* creation of the Knock-Out [constitutive, conditional] model (based on information available) will be evaluated specifically.

2. **Knock-In models:**

- Models will be generated by CRISPR/Cas9 (point mutation only) or ES cells for more complex design.
- For complex designs feasibility will be assessed.
- Only C57BL/6N genetic background is available.

3. **Transgenic models:**

- Only injections of a single transgene will be made.
- Generation of more than two lines and overexpression of the transgene cannot be guaranteed.
- Only C57BL/6N genetic background.

D – Scientific evaluation

Submitted projects will be evaluated by **two external referees** and then selected by a **scientific *ad hoc* committee**, composed of PHENOMIN and Scientific Advisory Board of the French Foundation for rare diseases members.

Evaluation criteria:

The following elements will be particularly considered in the evaluation of the project:

- Relevance and originality of the project;
- Relevance and quality of scientifically validated preliminary data;
- Relevance of the animal model for human disease;
- Integration of the project in the research program of the applicant;
- Positioning of the project in the national and international context;
- Clarity of objectives and outcomes of the project;
- Team experience in mouse model exploration and animal room facilities;
- Respect of animal ethical rules;
- Prospects in terms of future development and capitalization of emerging data.

E – Funding

Successful applicants will receive financial support for the establishment of the mouse model - Knock-Out [constitutive, conditional], Knock-In and transgenic mice - the expansion of the model (in case of standard phenotyping only) and phenotyping according to the standard scheme defined by the international consortium IMPC.
Funding will cover services costs provided by the platform and is not intended to cover equipment, running costs or personnel costs in the researcher's laboratory.

For successful applications, if a conditional Knock-Out model is under development at that time in another center from the IMPC consortium, the latter will not be generated again by PHENOMIN. Financial support will cover the cost of transfer of the model for a maximum amount of 3 000 €.

F – Proposal submission and schedule of the call

To complete and submit an application form, please access to the portal "**Applicant portal**".

Submission deadline for proposals: **January 31, 2017 (5:00 pm)**.

The provisional schedule of the call is the following:

December, 2016	Launch of the call
January 31, 2017	Submission deadline for proposals
February 2017	Technical feasibility assessment by PHENOMIN
March-April 2017	Scientific evaluation by two external referees
May 2017	Selection by the committee
June 2017	Publication of the selected projects

The title of the selected projects and name of their principal investigator will be published on the website of the French Foundation for rare diseases and PHENOMIN by December 2016. The summary written for a general audience may be used for communication purposes.

Results and Intellectual Property data resulting from projects funded through the call will be owned by the researcher's organizations.

Acknowledgement Policy: It is required that projects funded acknowledge the French Foundation for rare diseases and the PHENOMIN infrastructure in all publications and communications. Reference(s) of the publication(s) must be sent to the Foundation.

IRDiRC policies and guidelines: the project partners are expected to follow IRDiRC policies and guidelines. For more information see http://www.irdirc.org