Call 2013: 'Mouse models and rare diseases'

Fondation maladies rares and the French National Infrastructure **PHENOMIN**, which includes the Institut Clinique de la Souris (ICS, Illkirch), the Transgenesis and Archiving of Animal Models (TAAM, Orléans, Villejuif) and the Centre for Immunophenomics (CIPHE, Marseille) launch **a joint call for the creation and exploration of mouse models for rare diseases** (see the summary diagram in Appendix).

This call for proposals is dedicated to the **generation** of mouse models for rare diseases -conditional Knock-Out (cKO), Knock-In (KI) and transgenic mice-.
Conditional Knock-Outs will be primarily generated from ES cells derived from the international **IKMC resource** (www.knockoutmouse.org). If the ES clones are not available in this resource and if the line is not already under development in another IKMC resource center, the conditional Knock-Out can be generated *de novo* by the PHENOMIN infrastructure.
Knock-In mice (reporter gene, point mutation, humanization, but excluding complex modifications), as well as **transgenic mice**, will be generated ***de novo*** by the PHENOMIN infrastructure.

All conditional models derived from the IKMC resource will then be **phenotyped** according to a **standard scheme** defined by the international consortium **IMPC** members (www.mousephenotype.org). Models generated *de novo* by the PHENOMIN infrastructure can be phenotyped exclusively along the same scheme, at the request of the principal investigator and after a specific evaluation of the application.

Knock-Out models (with conditional potential) generated from the **IKMC resource**, as well as the related phenotypic data, will be made **available to the principal investigator and to the whole scientific community through the IMPC portal**. The IMPC international program provides a single web-based database thus referencing all resources available.
Models generated *de novo* by the PHENOMIN infrastructure will be **provided first to the principal investigator** and within 24 months to the scientific community. The IMPC standard phenotyping data will be made available to the community within 12 months.

Submitted projects will be evaluated by **two external referees** and then selected by a **scientific *ad hoc* committee**, composed of members of the PHENOMIN committee and from the Scientific Board of Fondation maladies rares.

Application forms are available on both websites of Fondation maladies rares (http://fondation-maladiesrares.org) and PHENOMIN (www.phenomin.fr) or upon request using: modeles_murins@fondation-maladiesrares.com. Each submitted form must be related to only one model.

Submission deadline for proposals is **February 28, 2013 (midnight)**. Application forms must be sent by email to: modeles_murins@fondation-maladiesrares.com and by post mail (two signed original copies).

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 genes have been identified.

The production of these models also meets **a key objective in the development of a therapeutic strategy**. When a therapeutic proof of principle has been identified and tested *in vitro*, it is necessary to test this therapeutic approach in a 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 prior to conducting early phases of a therapeutic trial.

PHENOMIN supports Fondation maladies rares in order to achieve these objectives and starts a 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 projects (see the summary diagram in Appendix)

This call for proposals is open to research projects covering **all rare diseases**, without restriction.

The principal investigator of the project must be attached to a **French research team**.

1- Generation of mouse models

a. Conditional Knock-Out mice:

Conditional Knock-Outs will be primarily generated from ES cells derived from the international IKMC resource (www.knockoutmouse.org). Models will be generated on a C57BL/6N genetic background. In some cases, conditional or constitutive Knock-Out models can be generated *de novo* by PHENOMIN, depending on the project.
Constitutive Knock-Outs (total deletion of genes from the ATG to the stop codon) can be generated from existing clones derived from the resource KOMP (www.knockoutmouse.org/aboutkompstrategies).

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.

Knock-In mice can be generated on different genetic backgrounds: C57BL/6N, BALB/cN, 129Sv/Pas.

c. Transgenic mice:

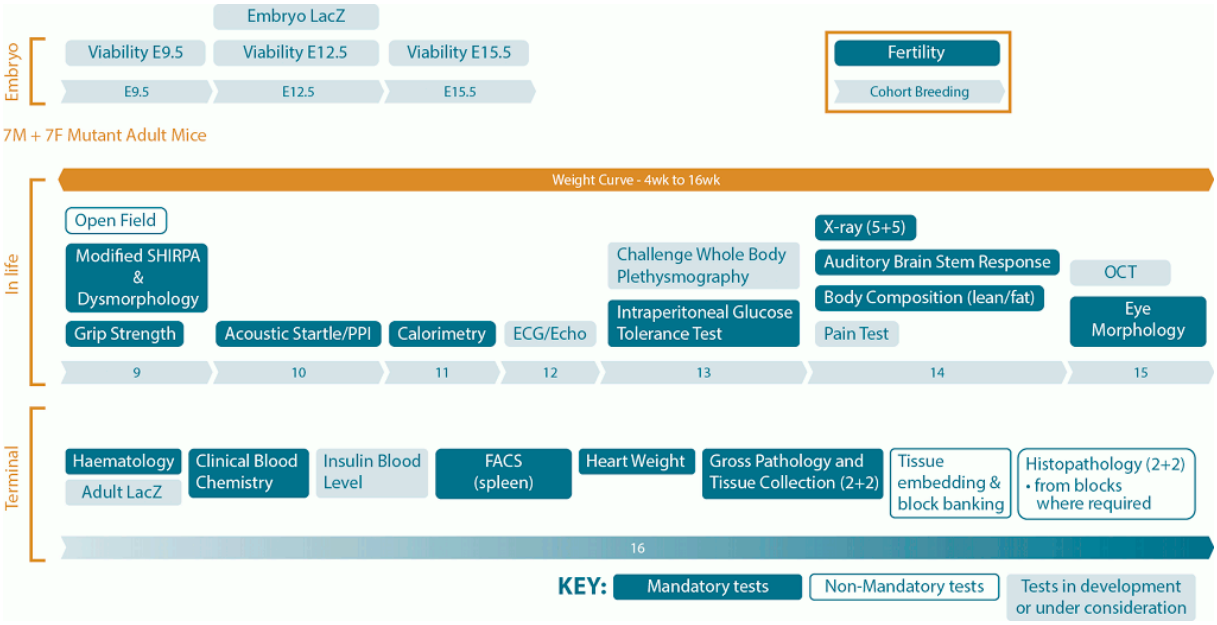
Transgenic mice (overexpression by pronuclear injection, but excluding complex constructs) will be generated *de novo* by the PHENOMIN infrastructure.

2- Expansion and phenotyping

All conditional models derived from the IKMC resource 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 expertise of the application -the added value to achieve a global standard phenotype will be evaluated- .

IMPReSS standard phenotyping scheme



3- Scheduling for models generation, phenotyping and data availability to the investigator and to the scientific community

Conditional Knock-Out models generated from the resource IKMC will be sent to the principal investigator of the project within 8 to 16 months after obtaining information and materials needed to start the project. In general, 80% of projects will be 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 IKMC clones or to achieve the targeting constructs.

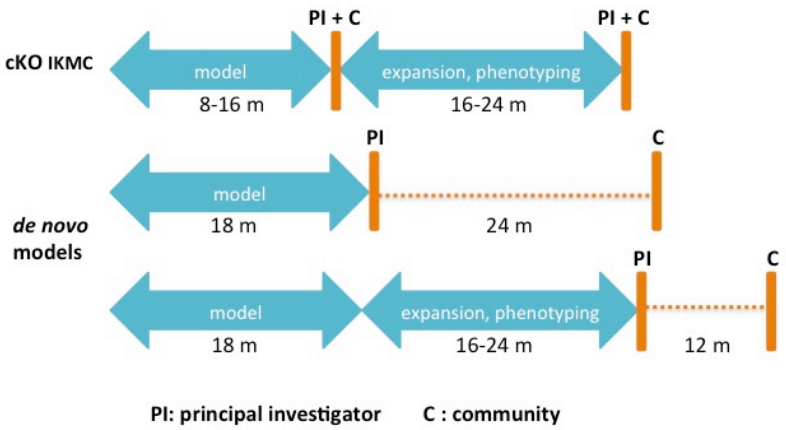
The progress of each project will be monitored and updated every 6 months by the PHENOMIN project manager and communicated to the principal investigator.

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

According to the IKMC consortium rules, **the generated Knock-Out models (with conditional potential) generated from this resource** 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 IKMC 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



C – Evaluation

1- Evaluation criteria:

- Relevance and originality of the project;
- 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.

2- Technical eligibility check:

a. Conditional models:

Several cases are possible.

- *Case 1: The model is available or is developed by another IKMC resource center.*
  In this case, the PHENOMIN infrastructure will establish connection between the principal investigator and the corresponding center, towards organizing the transfer of the model.

- *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 IKMC website (www.knockoutmouse.org).
  In this case, only the recombinant ES clones generated by the consortium IKMC will be used.

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

b. Knock-In models:

- For targeted mutations, projects will only be initiated if corresponding to a point mutation or several mutations in the same region.
- For humanization or reporter models, complex designs are not supported.
- Only C57BL/6N, BALB/cN and 129Sv/Pas genetic backgrounds are available.

c. Transgenic models:

- Only injections of a single transgene will be made. Complex constructs cannot be processed.
- Generation of more than two lines and overexpression of the transgene cannot be guaranteed.
- Only C57BL/6N and FVBN genetic backgrounds or hybrid of these 2 strains are available.

D – Funding

This call provides full financial support for the establishment of the mouse model - conditional Knock-Out, Knock-In and transgenic mice - the expansion of the model (in case of further phenotyping) and phenotyping according to the standard scheme defined by the international consortium IMPC.
If a conditional Knock-Out model is under development 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.

E – Proposal submission and schedule of the call

Application forms are available on websites of Fondation maladies rares (http://fondation-maladiesrares.org) and PHENOMIN (www.phenomin.fr) or upon request by using: modeles_murins@fondation-maladiesrares.com. One submission form per independent project must be submitted.

Schedule of the call for proposals:

- Submission deadline for proposals: **February 28, 2013 (midnight)**. Application forms must be sent by email to: modeles_murins@fondation-maladiesrares.com and by post mail (two signed paper copies) to: Fondation maladies rares, Appel à projets 'Modèles murins et maladies rares', 96 rue Didot, Plateforme Maladies Rares, 75014 Paris.

- Evaluation process :
  - Technical eligibility check by PHENOMIN (March 2013)
  - Evaluation by two external referees (March-April 2013)
  - Selection by a scientific *ad hoc* committee, composed of members of the PHENOMIN committee and of the Scientific Board of the Fondation maladies rares (May 2013).

- The title of the selected projects and name of their principal investigator will be published on both websites of Fondation maladies rares and PHENOMIN by June 2013.

Appendix: Summary diagram of the call