Call 2016: 'Small animal models and rare diseases'

The French Foundation for rare diseases (Fondation maladies rares) is pleased to launch, in collaboration with the French National Infrastructure TEFOR, its second call for proposals: development and study of small animal models -excluding mouse models- for rare diseases.

A – Context and aims of the call

A1. Presentation

The French Foundation for rare diseases (Fondation maladies rares) promotes and supports research on rare diseases. This Foundation was created in 2012, as a key feature action of the second French National Rare Disease Plan (2011-2014). It is operating with public and private sources of funding to stimulate, coordinate and support fundamental, clinical and translational research. Founders include the French Muscular Dystrophy Association (Association Française contre les Myopathies – AFM-Téléthon), Alliance Maladies Rares, the French National Institute of Health and Medical Research (Inserm), the Conference of General Directors of the French University Hospitals and the Conference of Presidents of French Universities. The Foundation plays a pivotal role, covering all domains of research in rare diseases, with a strong emphasis on translational research.

The Foundation promotes and supports research on rare diseases through specific calls for projects. In this context, one of the main objectives of the Foundation is to facilitate access for researchers to strategic technology platforms by providing financial support. All the scientific activities of the Foundation are directed by its Administrative Board, composed of presidents or representatives of the 5 founding organizations and 8 qualified individuals. The Foundation benefits from the guidance of a Scientific Advisory Board composed of internationally renowned physicians and scientists, key opinion leaders in the field of rare diseases.

TEFOR is a French infrastructure that promotes innovative services and tools for research on Drosophila, Zebrafish and other model organisms. TEFOR provides cutting-edge integrated services for transgenesis, genome editing and phenotyping. A growing number of academic platforms now facilitate access of research teams to innovative and rapidly evolving technologies applied to the generation of genetically engineered animals from a large panel of species.
TEFOR brings three platforms together: AMAGEN, dedicated to small fish, specially Zebrafish, the FLY FACILITY for the fly, and TRIP, the Rat transgenesis platform. Other national platforms give support for the generation and characterization of models in the xenopus (CRB, the Xenopus transgenesis platform) and the rabbit (the Rabbit transgenesis platform).

A2. Context

Animal models are essential tools to get insights into physiological processes and improve the understanding of molecular and cellular mechanisms leading to pathological conditions related to a rare disease. They have proven to be useful for the development of new diagnostic and therapeutic approaches.

Mouse models are common for the study of human diseases and have already demonstrated the extent of their impact. The French Foundation for rare diseases already supports research teams for the development and characterization of mouse models (Call mouse models and rare diseases).

However, some other small animal models could alternatively be used according to the 3R rule. They may present some close physiological similarities and better mimic a disease.

They may furthermore provide a number of exceptional advantages, such as to obtain quicker results, better monitoring and modeling of physiopathological processes that can only be followed *in vivo* and to perform integrated studies (-omics) and screening of phenotypic changes in response to genetic alterations (such as pangenomic screen) or small molecules.

Choosing an appropriate and reliable animal model is of particular importance. In some cases also, it can be advantageous to use several complementary animal models to cover different aspects of the same disease (transversal/integrative approaches). In addition, the use of one or more small animal models can represent a key step before the use of large animal models in the early stage of clinical applications, in order to validate *in vivo* a proof of concept.

Genome editing represents a technological revolution that allows the generation of animals modeling human diseases in every organism. Advances in the methodologies that can be applied to small animal models extend opportunities in rare diseases research and new avenues towards addressing therapeutic approaches.

A3. Objectives

This call aims to give a significant boost to the generation and characterization of small animal models of rare diseases, in order to get a better understanding of pathophysiological mechanisms involved in rare diseases and to provide evidence for therapeutic proofs of principle that may eventually be translated into rare diseases patients care.

Another objective of this call is to favor new collaborations between rare diseases research teams and groups with extensive experience with a particular animal model, helping the development of interesting and innovative models and the related functional studies, which would lead to significant advances in rare diseases research.

B – Content of the call

Successful applicants will have a facilitated access to tools developed by experienced academic platforms, in order to develop small animal models of rare diseases.
The precise type of model development (knock-out, knock-in, humanized model, transgenic…), will be specific to each organism, but will rely on the latest improvements and most appropriate techniques of genome editing (ZFNs, TALEN, CRISPR/CAS9, etc.) or more classical transgenic approaches (such as DNA microinjection, lentiviral infection). **The project must be based on scientifically validated preliminary data and the choice of organism and model must be clearly justified.**
Pilot functional studies may be considered if the relevant services are provided by the platform, for example: phenotyping by advanced imaging (zebrafish), etc.

In the scope of this call, animal models will be developed with the support of the following national platforms:
Non-mammalian models:
- Zebrafish, with the platform AMAGEN, Gif-sur-Yvette (TEFOR infrastructure);
- Fly, with the platform FLY FACILITY, Clermont-Ferrand (TEFOR infrastructure);
- Xenopus, with the platform CRB, Rennes;

Mammalian models:
- Rat, with the platform TRIP, Nantes (TEFOR infrastructure);
- Rabbit, with the transgenesis platform of INRA, Jouy-en-Josas.

Technologies and applications used by each platform for every organism, links to websites and contacts for each platform are listed in Annex 1.

Principal investigators must contact platforms for a detailed description of services that could fit the objectives of their project and to obtain assistance in optimizing the technical design. The technical validation of the project by the platform is mandatory. A detailed timetable and budget associated with each step of the project must be provided accordingly.
The progress of each project will be monitored and updated every 3 months by the project manager of the platform and communicated to the principal investigator.

Principal investigators may also seek advice from platforms in order to establish appropriate collaborations with teams specialized in the use of particular model species.

C – Evaluation

C1. Eligibility

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).

C2. Evaluation criteria

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

- Originality of the project;
- Relevance of preliminary data justifying the development of the model;
- Adequacy of the species and model for the human disease;
- Clarity of objectives and outcomes of the project;
- Prospects in terms of disease knowledge and expected therapeutic benefits;
- Detailed description and timetable of the research program proposed;
- Quality of the team;
- Integration of the project in the research program of the applicant;
- Team experience and complementary and synergy of associated partners in model exploration;
- Positioning of the project in the national and international context.

C3. Selection

Selection will be made on a peer review mode. Proposals will be evaluated by two external, national and international, academic referees with a recognized expertise on the model. Projects will then be selected by a scientific *ad hoc* committee, composed of small animal models experts and members of the Scientific Advisory Board of the French Foundation for rare diseases.

D – Funding

The French Foundation for rare diseases will provide financial support for the generation of the animal model and/or if justified and approved, for the characterization of the model by phenotyping or functional studies.
Funding will cover costs of **services provided by the platform** and is not intended to cover equipment, running costs or personnel costs in the researcher's laboratory.

E – 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: **July 5, 2016 (5:00 pm)**.
The provisional schedule of the call is the following:

April, 2016	Launch of the call
July 5, 2016	Submission deadline for proposals
September-October 2016	Evaluation by two external referees
November 2016	Selection by the committee
December 2016	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 by December 2016. The summary written for a general audience may be used for communication purposes by the Foundation and TEFOR.

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 TEFOR 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

ANNEX 1: PARTNER PLATFORMS OF THE CALL

Fly Facility

organism(s)	*Drosophila melanogaster*
localization	GReD, INSERM U1103, CNRS UMR6293, Université d'Auvergne, Clermont-Ferrand
website	www.fly-facility.com
contacts	contact@fly-facility.com Christophe Jagla: christophe.jagla@udamail.fr Teresa Jagla: teresa.jagla@udamail.fr
phone	04 73 17 81 81
applications	U6-sgRNA transgenic strains development gRNA efficiency tests in embryos KO and KI models
technologies	CRISPR/Cas 9 Transgenesis

AMAGEN

organism(s)	*Danio rerio* *Oryzias latipes*
localization	UMS CNRS/INRA Gif-sur-Yvette and Jouy-en-Josas
website	http://www.inaf.cnrs-gif.fr/inaf/amagen.html
contacts	Frédéric Sohm amagen@inaf.cnrs-gif.fr
phone	01 69 82 34 12
applications	KO and KI models Transgenic strains, including Gal4 strains Phenotyping by advanced imaging (Tefor core facility)
technologies	CRISPR/Cas 9 microinjection TALEN microinjection DNA microinjection Imaging technics (via TEFOR Core Facility)

CRB Xénopes	
organism(s)	*Xenopus laevis* *Xenopus tropicalis*
localization	UMS 3387 CNRS/Université de Rennes 1 - 263, avenue du Général Leclerc F-35042 Rennes Cedex
website	http://xenopus.univ-rennes1.fr
contacts	crb-xenopes@univ-rennes1.fr Daniel Boujard: daniel.boujard@univ-rennes1.fr Christophe Heligon : christophe.heligon@univ-rennes1.fr
phone	02 23 23 52 50 02 23 23 52 51
applications	KO strains transgenic strains
technologies	CRISPR/Cas 9 microinjection TALEN microinjection DNA microinjection Genotyping

TRIP-Nantes	
organism(s)	*Rattus norvegicus*
localization	INSERM UMR 1064, 30, boulevard Jean Monnet, 44093 Nantes
website	http://www.tgr.nantes.inserm.fr/
contacts	Ignacio Anegon: Ignacio.Anegon@univ-nantes.fr Séverine Ménoret: severine.menoret@univ-nantes.fr
phone	02 40 08 74 15
applications	Generation of transgenic by small or large (BAC) DNA microinjection Generation of KI or KO rats Immunophenotype
technologies	DNA, ZFNs, TALENs, CRISPR/Cas9, PiggyBac transposon and lentiviral vectors microinjection Embryo freezing Q-PCR genotyping (zygosity animals) Identification of transgenes integration site (LM-PCR) Analysis of immune responses

Atelier de modification génétique chez les mammifères non rongeurs	
organism(s)	*Oryctolagus cuniculus* (New Zealand rabbits, NZ 1077)
localization	INRA UMR 1198 Biologie du Développement et Reproduction 78350 Jouy en Josas
website	http://www6.jouy.inra.fr/bdr/Services-communs/Ateliers
contacts	Geneviève Jolivet genevieve.jolivet@jouy.inra.fr
phone	01 34 65 25 44
applications	Production of transgenic rabbits (additive transgenesis) KO, KI, siRNA mediated knock down Design of transgene, TALEN, gRNA Phenotyping investigation
technologies	DNA, RNA injection, BAC DNA injection TALEN, ZFN, CRISPR technologies Genotyping (PCR, cloning of transgene integration sites) Ultrasound analysis, iDEXA -Dual X-ray Absorptiometry