FONDATION
Maladies Rares

2022 Call 'Development of experimental models for rare diseases'

Foundation For Rare Diseases (Fondation Maladies Rares)

A – Context and aim of the call

Genome editing and advances in associated methodologies represent a technological revolution that extends opportunities in rare diseases research and new avenues towards addressing pathophysiological and therapeutic approaches, by allowing the development of models for the investigation of human diseases. This call aims to give a significant boost to the **development of new experimental models of rare diseases**, in order to:

- improve the understanding of molecular and cellular mechanisms leading to pathological conditions related to a rare disease,
- provide evidence for therapeutic proofs of principle that may eventually lead to treatment.

The project must directly rely on the study of one/several rare disease(s). The rationale of the proposed model must be robust enough for a better understanding of the pathophysiological mechanisms or for answering a key objective in the development of a therapeutic strategy related to the targeted pathology. Prior to developing the model, functional studies should have been performed to demonstrate the pathogenicity of the mutation involved or the networks linking the causative gene to the disease.

New collaborations between rare diseases research teams and groups with extensive experience with a particular animal model are encouraged to help the development of interesting and innovative models and related functional studies, which would lead to significant advances in rare diseases research.

Choosing an appropriate and reliable experimental model is of particular importance and must be guided by obtaining results that best mimic human pathology. In some cases, it can be advantageous using several complementary models to cover different aspects of the same disease (transversal/integrative approaches) and/or reach distinct objectives. In addition, the use of one or more experimental models is essential to validate a proof of concept in order to bridge the translational gap between preclinical and clinical research.

Mouse models are widely and the most commonly used for the study of human diseases and have already demonstrated the extent of their impact. However, in some cases, the **rat model** offers better clinical characterization approaches than the mouse model; its larger size allows to perform several experiments and surgical procedures and to monitor physiological

parameters. Because rats share many physiological similarities with humans, the rat has long been a model favoured by physiologists, pharmacologists, cardiologists and neuroscientists.
Some **other small animal models**, such as zebrafish, could alternatively be used because they may present some close physiological similarities and better mimic a disease. They may furthermore provide a number of advantages, such as obtaining quicker results, better monitoring and modelling of physiopathological processes that can only be followed *in vivo* and performing integrated studies (-omics) and screening of phenotypic changes in response to genetic alterations (such as pangenomic screen) or small molecules.
New technologies contribute to the respect of the 3R rules which aim at reducing the number of used animals and at replacing them when suitable and are now leading to new solutions to optimize the application of the rules.
Disease-specific **induced pluripotent stem cells (iPSC)** can be generated from patients with rare diseases, providing an effective approach for disease modelling and drug discovery and the opportunity to study a cellular response in a closed system, where the experimental conditions are maintained. The iPSCs provide a unique way for observing associated phenotypes and therapeutic screening to different genetic variants. The development of *in vitro* models as substitutes to animal models may allow optimising the reproduction of physiological/pathophysiological processes *in vivo* (ex: 2D, 3D, iPSCs, organoids, etc.)

In order to achieve the objective of **generating new experimental models dedicated to rare diseases,** the Foundation for Rare Diseases has set up partnerships with:
- CELPHEDIA (Creation, Breeding, Phenotyping, Distribution and Archiving of model organisms), the French infrastructure that promotes innovative services and tools on model organisms dedicated to the generation of disease models,
- experienced national platforms or companies including the ones giving support for the generation and characterization of models in the nematode *C. elegans* (Biology of *C. elegans* and *C. elegans* functional genomics).,
- the iPSC Nantes platform, for the development of disease-specific induced pluripotent stem cell (iPSC) lines.

All these partners offer an outstanding range of expertise, skills and services, provide advice to select **the most appropriate experimental model**, and answer the common objective to develop **model resources** that will be made available to the scientific community.

B – Content of the call

The project must be based on scientifically validated preliminary data and the choice of the experimental model must be clearly justified. The call is dedicated only to generating new experimental models for rare diseases (including conditions for archiving lines). Any other request (breeding, phenotyping, advanced imaging, etc.) is not eligible.

Successful applicants will have a facilitated access to tools proposed by experienced platforms to develop new experimental 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 (CRISPR/CAS9, etc.) or more classical transgenic approaches (such as DNA microinjection or lentiviral infection).
For the development of *in vitro* models based on induced pluripotent stem cell (iPSC) lines, the best suited approach will be designed for each project. Please pay attention that only projects for which agreements of lineage derivation from iPS of patients have already been obtained will be considered.

Only one project per research team can be funded for the current call.

In the scope of this call, non-mammalian and mammalian animal models will be developed with the support of the national platforms or companies, most of them being part of CELPHEDIA, the French infrastructure that promotes innovative services and tools on model organisms: https://fondation-maladiesrares.org/les-plateformes/

For animal models, if specific needs are not covered by partner platforms, please contact the Foundation at **aap-bio@fondation-maladiesrares.com** in order to evaluate the eligibility of the proposed model and conditions of services. In any case, technical issues must have been discussed with platforms to ensure the feasibility of the project. The model will be developed with the support of a platform.

Human induced pluripotent stem cell (iPSC) lines will be developed with the support of the Platform iPSC Nantes.

Technologies and applications used by each platform, links to websites and contacts for each platform are available on the website (https://fondation-maladiesrares.org/les-plateformes/).

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 eligibility of the project must be checked and approved by the platform before

submission. This procedure should be planned early in the process in order to ensure timely submission of the project.
An additional delay of 4 weeks is planned after the submission, in order to allow discussions between the PI and the platform, in order to optimize if necessary, the experimental design and to receive **technical validation of the project by the platform, which is mandatory.**

Please confer to each platform to be informed of model distribution rules to make models available to the whole scientific community.

C – Evaluation

C1. Eligibility
The principal investigator of the project must belong to a **French academic research team** working in universities, other higher education institutions or research institutes, and/or to the clinical/public health sector (university hospitals/public health organizations).
For the development of iPS cell lines, please pay attention that only projects for which agreements of lineage derivation from iPS of patients have already been obtained will be considered.

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 proposed 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/synergy of associated partners in model exploration;
- Positioning of the project in the national and international context.

C3. Selection
Proposals will be evaluated by at least two external, national and international, academic referees with a recognized expertise on the model. Projects will then be selected by a scientific committee composed of experimental models experts and members of the Scientific Advisory Board of the Foundation for Rare Diseases.

D – Funding

The Foundation for Rare Diseases will provide financial support only to cover the costs of **services provided by the platform** and will not cover equipment, running costs or personnel costs in the researcher's laboratory. Overheads are not eligible costs.

E – Proposal submission and schedule of the call

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

Requirements for full proposals

* *Applicants resubmitting projects are required to provide a detailed answer to the comments provided by the FFRD Scientific Committee at a previous session and highlight changes in the revised version.*
* *Applicants who were previously funded by the FFRD are required to provide a detailed report on the results and impacts of all ended projects. For ongoing projects, a detailed progress and / or preliminary data report is required. This reporting (free format) is mandatory.*

Submission deadline for proposals: **September 15, 2022 (5:00 pm)**.
The provisional schedule of the call is the following:

June, 2022	Launch of the call
September 15, 2022	Submission deadline for proposals
September 30, 2022	Technical validation by platform
October-November 2022	Evaluation by two external referees
December 2022	Selection by the committee

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 mid-december 2022. The summary written for a general audience may be used for communication purposes by the Foundation.

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 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