Call 2021
'Identifying therapeutic molecules for rare diseases'

The call '**Identifying therapeutic molecules for rare diseases'** launched by the French Foundation for Rare Diseases (Fondation Maladies Rares) will support one of the two following steps of **drug discovery**:

1. **Development of an automated assay and compound screening**
2. **'Hit to Lead' campaign to develop lead candidates**

Submission deadline for proposals: January 20, 2022 5:00 pm

A – Context and objectives of the call for proposals

Development of therapies for patients living with a rare disease is an absolute priority, since for most rare diseases, no pathophysiology-based therapy nor efficient treatment exist.

The French Foundation for Rare Diseases launches a call for proposals to support projects aimed at identifying molecules with potential benefit in the treatment of rare diseases.

Two steps of drug discovery will be considered:

1. Projects will either rely on a high throughput/content screening (HTS/HCS) approach using compound libraries, towards the discovery of active molecules 'hits' with therapeutic potential.
   The development of the miniaturized robust and reproducible assay is considered as a crucial step and a starting point in the process of filtering out potential 'hits' to be optimized as downstream drug candidates. Moreover, the experimental design of the screening, which has key consequences on the quality of the subsequent hits selected, requires the expertise of HTS trained staff.

2. Another step towards investigating into the 'hit to lead' process to approach drug-like characteristics can be supported.
   At this stage, the crossroads of all skills between the medicinal chemist and the biologist, multidisciplinary teams and competences in pharmacokinetics, physico-chemistry, toxicology, chemo-computing in order to evaluate all the parameters to be optimized will allow to select best compounds with drug-like characteristics.

B – Content of the call

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

For rare cancers, only projects concerning benign tumors as well as systemic rare diseases involving tumor development will be evaluated within this call.

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

B1. Development of an automated assay and compound screening

Prerequisite: The project must rely on scientifically validated preliminary data. The biological model (target/process/phenotype) **will have been identified and validated by the research team** itself or as part of a collaborating consortium or network. **Research studies must have allowed to validate an experimental model** reproducing a physiological, metabolic or biochemical pathway in the disease process for which read-outs are clearly defined. Then, the project must clearly emphasize the relevance of the screening assay towards the identification of molecules to reverse the pathogenesis of the disease described.

Assay development:
The knowledge gained as a result of the biological model validation process will evolve into a scheme for the development of an assay to be used in high throughput / content screening.
The establishment of the assay is based on two major tasks: miniaturization and automation. This requires downscaling the experiment to adapt it to a multi-well plate (96/384 wells) format for easy automation (pipetting, detection system). For that purpose, it is also necessary to adapt biochemical, cell culture or whole organism assay conditions and the assay read-out conditions.
The optimal conditions for implementing this strategy must be tailored for the model and take into account:
- the type of assay: target or process based; biochemical, cell-based (cell lines, differentiated primary or induced pluripotent stem cells - disease-specific and control) and, when possible, validation in whole organism-based assay; the biological model and the link between the model and the aimed pathology
- the detection technology employed (e.g. luminescence, fluorescence, etc.)
- reagents required (e.g. cell lines, antibodies, purified proteins, enzyme substrates, etc.)
- equipment required

Clear and measurable read-out(s) must have been identified.
Successful applicants will have the opportunity to develop a small-scale high throughput / content screening assay as a first step.

Compound screening:
The screening of the Prestwick chemical library [1520 small molecules, FDA approved active compounds selected for their high chemical and pharmacological diversity, known bioavailability and safety in humans] or of an equivalent library may be envisaged in order to validate the assay and to allow picking 'hits'. The screening of larger chemical/natural libraries (~10,000 compounds), such as a part of the French National Chemical Library, could be performed on the fully operational system.

B2. 'Hit to Lead' campaign to develop lead candidates

Prerequisite: for investigators who already identified promising hits from a screening campaign.

'Hit to lead' optimization stages follow the identification of primary hits from screening and rely on two major steps:

1- Hits confirmation and profiling
Objective: confirm a limited series of molecules, by complementary approaches such as confirmatory testing, dose response curves, orthogonal testing, biophysical testing, secondary screening, giving prioritization through multiple criteria such as patents, synthesis pathways, *in silico* profiling, etc., with the aim to rank and cluster hits.

2- Lead discovery

Objective: to evaluate the optimization potential of confirmed hits in order to select the best compounds and to provide a limited optimization of selected compounds towards a proof of concept in an animal model by combining experimental and computer-aided protocols.

May include for example:
- the validation of hits or candidate drugs (not necessarily from screening, but already identified in publications) in models of the disease.
- the evaluation of pharmacology (activity/efficacy) and physico-chemical profiles, ADME (Absorption, Distribution, Metabolism, Excretion) and toxicology properties, pharmacokinetic (PK) behavior;
- a limited testing (minimum 3) of analogous compounds to determine a quantitative structure-activity relationship (QSAR);
- the improvement of hits affinities, metabolic half-life, selectivity against other biological targets.

C- Conditions of experimentation

C1. Access to platforms

Principal investigators must contact platforms for a detailed description of services and costs that could fit the objectives of their project and to obtain assistance in optimizing the technical design: assay miniaturization/automation, choice of chemical libraries to screen, data analysis in 'hit' selection and validation, 'hit to lead' optimization stages. The technical eligibility of the project can thus be verified and approved by the platform.

The development of the miniaturized assay and the screening will be performed by an experienced academic HTS/HCS platform.
Screening platforms, the French infrastructure ChemBioFrance and private companies will provide advices and services for the best suited ADME/PK or chemistry approaches required for 'hit to lead' development schemes.

Information about technological partners of the call is available on the website (https://fondation-maladiesrares.org/les-plateformes/).

Other partnerships between the French Foundation for Rare Diseases and platform(s) will remain an exception. It will be considered on the basis of case-by-case evaluation by the Foundation in accordance with specifications of the call.

Applicant or head of platforms are invited to contact the Foundation at aap-bio@fondation-maladiesrares.com in order to evaluate partnership modalities or for any other question.

The assay will be developed in close interaction between dedicated member(s) of the research team and the platform.
A period of 6 to 18 months is required for assay development and screening.
A period of 6 to 18 months is required for hit selection and characterization (early ADME properties, analog testing).
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.

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

C2. Technical validation

An additional 4-week extension is planned after the submission, in order to allow **discussions between the PI and the platform**, to **optimize** if necessary, **the experimental design** and to receive **technical validation of the project by the platform, which is mandatory.**

A detailed timetable and budget associated with each step of the project must be provided.

D – Scientific evaluation

D1. 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 hospitals/public health organizations).

D2. Evaluation criteria

- Relevance of the project and robustness of preliminary data and the overarching scientific plan;
- Originality and/or innovative potential of the project;
- Feasibility of the project;
- Clarity of objectives and outcomes of the project;
- Prospects in terms of future development and capitalization of emerging data;
- Integration of the project in the research program of the applicant;
- Positioning of the project in the national and international context.

D3. Selection

Selection will be made on a peer review mode. Proposals will be evaluated by two external, national and international, referees with a recognized expertise in the area. Projects will then be selected by a scientific *ad hoc* committee, composed of platform representatives and members of the Scientific Advisory Board of the French Foundation for Rare Diseases.

E – Funding

The French Foundation for Rare Diseases may provide financial support for every of the following stages: the assay development and screening or the 'hit to lead' process for investigators who already identified promising hits from a screening campaign.

E1. Assay development and screening - for a maximal amount of 25,000€ - for the setting up and validation of a miniaturized assay, the primary high throughput screening of a medium-scale chemical/natural compound library (~10,000 compounds), hit confirmation, dose-response and a report of results provided by the screening platform.

E2. 'Hit to Lead' campaign - for a maximal amount of 25,000€ - for investigating into the 'hit to lead' process by experimental and *in silico* approaches.

Funding will cover operating costs (services and consumables) but is not intended to cover equipment or personnel costs in the researcher's laboratory.

F – 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: **January 20, 2022 (5:00 pm)**.

The provisional schedule of the call is the following:

December 2, 2021	Launch of the call
January 20, 2022	Submission deadline for proposals
February 24, 2022	Technical validation by platform
March-April 2022	Evaluation process
May 2022	Publication of the selected projects

The title of the selected projects and name of the principal investigator will be published on the website of the French Foundation for Rare Diseases. The summary written for a general audience may be used for communication purposes by the Foundation.

Acknowledgement Policy: it is required that projects funded by the French Foundation for Rare Diseases be acknowledged 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