Call 2016: 'High throughput screening of therapeutic molecules and rare diseases'

The third call 'High throughput screening of therapeutic molecules and rare diseases' launched by the French Foundation for rare diseases (Fondation maladies rares) will support specifically early phases of drug discovery, by focusing on the use of high throughput screening for 'hit discovery'.

Submission deadline for proposals: March 31, 2016, 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.
Considering the lack of therapeutic proofs of principle in rare diseases, the French Foundation for rare diseases launches a call for proposals dedicated to 'High throughput screening of therapeutic molecules'. Through this call, the French Foundation for rare diseases will support projects aimed at identifying molecules with potential benefit in the treatment of rare diseases. So far, it is being considered that in many cases, such identified molecules have been transfered into clinical trials; in rare situations, they have obtained orphan drug designation while only a few of them have obtained market approval. In this context, several past experiences have demonstrated high throughput screening (HTS) as a valuable tool to identify efficient molecules.

A key challenge in rare diseases is to identify small molecules that are effective at modulating a given biological process or disease state and high throughput screening of small molecules meets several objectives in basic, translational and clinical research. Small molecules have proven to be irreplaceable tools to evaluate the improvement or modification of defective functions that can be explored *in vitro* as well as in living models. Such molecules could also represent pharmacological leads for treating diseases.

In the context of the present call, projects will be based on a high throughput screening approach using compound libraries, towards the discovery of active molecules 'hits' with therapeutic potential.

A first observation made is that the success rate in setting up a screening assay of an identified biological model is very low. The development of the miniaturized robust and reproducible assay is then 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.
The success of this step can be greatly enhanced by taking advantage of the expertise and equipment of an experienced HTS platform.

Once a proof of concept of an HTS assay is validated, the latter constitutes an excellent lever for applying for larger projects and finding partners to support the development of a large scale screen. It represents the first solid basis towards the identification of new candidate drugs.

B – Content of the call

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

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

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).

Assay development and screening: 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 developing a high throughput screening assay as a first step towards identification of small molecules to reverse the pathogenesis of the disease described.

The knowledge gained as a result of the biological model validation process will evolve into a scheme for the development of an assay model to be used in high throughput screening.
The establishment of the HTS assay is based on two major tasks: miniaturization and automation. This requires downscaling the experiments to adapt them 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 *in vivo* 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 or 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, …)
- reagents required (e.g. cell lines, antibodies, purified proteins, enzyme substrates…)
- 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 screening assay as a first step to confirm that the HTS method is operational. This proof-of-concept is essential to ensure optimal and high quality data results and if necessary, to adjust parameters before performing a larger screen.
The screening of the Prestwick chemical library [about 1,200 small molecules, FDA approved active compounds selected for their high chemical and pharmacological diversity, known bioavailability and safety in humans] or equivalent may be first 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 then be performed on the fully operational system.

Downstream stages of the drug discovery process, namely 'Hit to Lead' campaign to develop lead candidates [in this phase, 'hits' are subjected to improvements in their chemical properties such as solubility, permeability, stability… to approach drug-like characteristics and being designated as 'leads'] and perform 'Lead optimization' to develop drug candidate [new analog with improved potency, reduced off-target activities and physicochemical/metabolic properties for reasonable in vivo pharmaco-kinetics to prepare it for pre-clinical development] are excluded from the scope of the call.

Access to HTS partner platform: the development of the miniaturized HTS assay and the screening will be performed by an experienced academic HTS platform.

The selection of the platform is performed according to the relevance and orientation of the project and in order to allow optimization of the handling of projects by the platform, according to its expertise, technical specificity, equipment, capacity and calendar, with the aim to deliver optimal results to the research team.

The project shall be developed in close interaction between dedicated member(s) of the research team and the HTS platform.
A period of 6 to 18 months is required for assay development and screening.
The progress of each project will be monitored and updated every 3 months by the project manager (HTS 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.

C – Technical validation

Technical feasibility and eligibility of the project must be checked and approved by the platform before submission.

Information about HTS platforms partners of the call are available on the website (professional access; http://fondation-maladiesrares.org/appels-a-projets-clos).

Other partnerships between the French Foundation for rare diseases and HTS platform(s) can be considered in order to harmonize specific needs of applicants for their projects with services platforms, in accordance with specifications of the call.

Applicant and head of plateforms are invited to contact the Foundation at criblage_preclinique@fondation-maladiesrares.com in order to evaluate partnership modalities.

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.

The technical validation procedure is mandatory and should be planned early in the process in order to ensure timely submission of the project.

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

D – Scientific evaluation

1. Evaluation criteria

- Feasibility of the project;
- Relevance and originality of the project;
- Relevance of the screening 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;
- Prospects in terms of future development and capitalization of emerging data.

2. 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. Projects will then be selected by a scientific *ad hoc* committee, composed of HTS platform representatives and members of the Scientific Advisory Board of the French foundation for rare diseases.

E – Funding

The French Foundation for rare diseases will provide financial support - 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 HTS platform.

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.

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: **March 31, 2016 (5:00 pm)**.

The provisional schedule of the call is the following:

January, 2016	Launch of the call
March 31, 2016 (5:00 pm)	Submission deadline for proposal (electronic form)
April-June 2016	Evaluation process
July 2016	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