REQUEST FOR APPLICATIONS
TACKLE RARE, ORPHAN CFTR MUTATIONS
COMPETITION

June 2024

1. Overview

Cystic fibrosis exhibits a notably higher prevalence among the French-Canadian population in the Saguenay-Lac-Saint-Jean region of Québec. In fact, the average incidence of cystic fibrosis carriers in this region is estimated to be 1 in 15 people, compared to the national average of 1 in 30 people. Novel therapeutic agents aim to restore the proper function of cystic fibrosis transmembrane conductance regulator (CFTR) protein, providing significant benefits to numerous individuals living with cystic fibrosis. However, over 10% of mutations fail to produce any functional CFTR proteins, rendering these new treatments ineffective. In addition to having no treatment option, some of these rare mutations are underserved by scientific research exacerbating the inequality for the persons carrying these mutations. Genetic profiling of people affected by cystic fibrosis reveals that several of these rare mutations are especially prevalent in Québec (for example, the splicing mutations 621, 711). Individuals with these rare mutations are at risk of being left behind with no variant-specific modulator therapy.

To address this challenge, Génome Québec and Cystic Fibrosis Canada launch the *Tackle rare, orphan CTFR mutations* competition to support research on rare mutations for which no treatment is available with the long-term goal of developing novel therapies. This competition targets research proposals that have the potential to improve, in an inclusive manner, the well-being of all people affected by cystic fibrosis, thus contributing to the democratization of research while increasing public awareness. In addition, the competition aims to mobilize the Québec research community, while ensuring that the needs of the cystic fibrosis community are taken into account. **This competition is open only to researchers affiliated with an eligible institution in Québec (see section 4).**

2. Objectives

This call targets applications that support the following objectives:

- Specifically address forms of cystic fibrosis caused by rare mutations which are not responsive to currently available treatments[*1] and thereby take forward the Cystic Fibrosis community priorities.
- Improve the understanding of the mechanism of these mutations and/or lay the basis for development of novel therapies, using *omics*[*2] approaches.

3. Available funding, terms and conditions

- The total funding envelope for the competition is $1,200,000. Each team may request a total budget from $300,000 up to $600,000.
- The duration of the funded projects is three (3) years (project start date: April 1, 2025).
- Conditions:
  - Disbursement of funding is conditional to fulfillment of conditions and respect of terms mentioned in the notice of awards, including the signing of an agreement between Génome Québec and any institution participating in the research. Génome Québec reserves the right to withdraw the funding for any approved project not having fulfilled above conditions by March 14, 2025.

*1 Eligible mutations are class I mutations (nonsense, frameshift, splicing) that don't produce functional CFTR protein.

*2 *Omics*: Designates studies that use high-throughput technologies to gather genetic information of a cell or an organism, including the function of specific genes, their interactions, and the activation and suppression of genes. The definition also encompasses certain related disciplines, such as gene editing, gene therapy, epigenomics, metabolomics, metagenomics, nutrigenomics, pharmacogenomics, proteomics, transcriptomics, and bioinformatics. Studies that integrate data from medical imaging, electronic health records or portable devices are welcome, if they relate to *omics* data.

- As a matter of principle, Génome Québec encourages sharing the results of funded research in a timely manner, including open access to publications, the dissemination of data, and the sharing of resources with the scientific community. Rapid access to the results of projects funded by Génome Québec will accelerate research to benefit the public. In this context, Génome Québec encourages publication in peer-reviewed journals, in online directories, appropriate public databases, or journals ensuring free access within 12 months following publication. The following Tri-Agency policies should guide the dissemination of results as well as the management and sharing of data:
  - Open Access Policy on Publications
  - Research Data Management Policy

  Génome Québec recognizes the importance of ensuring the confidentiality of commercially sensitive information and seeks to strike a balance between openness and the protection of intellectual property. Candidates can thus request an exemption from the data-sharing requirements for the purposes of allowing the commercialization of research results. These requests will be evaluated by Génome Québec, and candidates will be informed of the decision in a timely manner.

4. Eligibility

- **Objectives:** The application must correspond to the competition's objectives (see section 2).
- **Supported themes and activities include, but are not limited to:**
  - Gene therapy and gene editing approaches, including those using and those targeting either RNA or DNA molecules. This also includes *ex vivo* correction prior to reimplantation.
  - Therapy targeting post-transcriptional RNA processing (including splicing) or translation (including proteomics methods).
  - Small molecule therapy development, if using *omics* technologies (ex: investigating mechanism of action or testing effects in established models using *omics* approaches).
  - Research involving induced pluripotent stem cells.
  - Generate initial evidence in established models prior to formal preclinical studies in anticipation of first-in-human clinical trials.
  - Innovative therapeutic and delivery approaches using nanotechnology.
  - Novel delivery methods that target airway cells of interest for cystic fibrosis gene delivery (ionocytes, basal cells, etc.).
  - Design of novel RNA structures for improving the delivery of antisense RNA to the lung for the benefit of people affected by cystic fibrosis.
  - Strategies to precisely control gene replacement or gene editing by exposure to small-molecule inducers.
  - Understanding molecular mechanisms of disease related to the rare mutation studied.
  - Target identification.
  - Studies of proteomic and metabolomic profiles.
  - Identification of biomarkers as a diagnostic tool to predict effect of a potential treatment.

  Note: The following studies are not eligible for this call:
  - Studies aimed solely at identifying new mutations (ex: sequencing studies).
  - Applications dedicated entirely to acquisition of samples.
  - Studies on modulation of other proteins to compensate for lack of CFTR function (Mutation agnostic approaches that could have equal benefit for F508del or other more common mutations).
- **Institutions, researchers and team:** In order to receive funds, researchers and institutions must meet the eligibility criteria set out in the *Génome Québec Financial Guidelines* (Appendix I).
  For this competition, a project leader can only submit (1) one application in a leadership role (includes administrative project leader and additional project leader).

People affected by cystic fibrosis, their caregivers or other community members can take part in projects as collaborators. Note that while inclusion of or co-creation with the community is encouraged, having a community member participate directly in the project team is not a requirement for this competition.

- **Localisation:** This competition is open only to researchers affiliated with a Québec-based university and affiliated institutions (including hospitals and research institutes), along with researchers affiliated with Québec-based colleges, college centres for the transfer of technology (CCTT) or non-for-profit organizations with an explicit research mandate.
  The funds can be awarded only to eligible organizations based in Québec. However, sharing resources and expertise in the form of collaborations, both at the national and international level, is encouraged.

For any other inquiries regarding eligibility, please contact: R-CFTR@genomequebec.com

5. Equity, diversity and inclusion

We understand that the quality of *omics* research is improving, and solutions provided by it become more comprehensive when different perspectives and expertise are brought together, providing room for a variety of views and ideas.
This funding opportunity allows multidisciplinary teams to bring different voices to the table and work on the principles of equity, diversity, and inclusion (EDI) to improve the impact of the research project, not only in terms of scientific deliverables, but also in terms of the impact on individuals working on these solutions and those who will implement and benefit from them. We invite teams to consider and focus on EDI challenges specific to their research project.
We recommend that teams consult the guide on integrating EDI considerations (Appendix II) and the evaluation criteria for this competition (Appendix III).

6. Application process

The application process includes two steps: a mandatory registration, and the application step only open to the registered project propositions deemed eligible (see section 4). All required documents must be sent by email, by the deadlines outlined in section 8, to R-CFTR@genomequebec.com. Génome Québec reserves the right to withdraw incomplete registration or application documents from the competition. The review process is detailed in section 7.

Required documents:

- **Registration form**
- **Application form** (including budget and statement(s) of work for external services budgeted)
  Note: The application form will be provided only after notice of eligibility of the registration.

7. Review process

To guarantee the funding of high-quality research proposals and to ensure that the competition's objectives are met, applications will be submitted to an independent evaluation committee ("the committee") whose members will be jointly selected by Génome Québec and Cystic Fibrosis Canada. This committee will consist of international scientists chosen based on their expertise (in the context of disease mechanisms, genetics, therapy, *omics* technologies and/or cystic fibrosis), an equity, diversity, and inclusion ("EDI") expert, as well as community reviewers (people living with cystic fibrosis or parents or spouses of someone living with cystic fibrosis).

The committee will evaluate the merit of the applications based on the criteria listed in the request for applications (see Appendix III).

The evaluation process will be organized jointly by Génome Québec and Cystic Fibrosis Canada, which are committed to providing a peer review process that meets the highest standards in terms of fairness, equity, and effectiveness. Prior to the review, all committee members will be asked to complete the virtual training module on *bias in peer review* by the Canadian Institutes of Health Research. The committee will meet virtually and make a funding

recommendation based on the scores determined for each application. The committee meeting procedures will follow best practices, including the respect of Génome Québec's rules pertaining to conflict of interest. Members of the funding organizations, along with other invited individuals from the Ministère de l'Économie, de l'Innovation, et de l'Énergie (MEIE), will participate only as observers to bear witness to the integrity of the review process.

APPLICATION REVIEW

The application review procedure will consist of three elements:

- For the scientific review, each application will be assigned to three scientific reviewers. Before the committee meeting, the reviewers will provide a written review, including a score, for each application assigned to them. These individual written reviews will be submitted to the other scientific and community reviewers before the committee meeting. Applications having received three individual scientific scores below 70 points will be streamlined and not discussed during the committee meeting.
- The score from the scientific reviewers will be calculated on a total of 95 points. The EDI section will be reviewed and scored separately prior to the committee meeting by an EDI expert. The EDI score will be calculated on a total of 5 points and added to the scientific reviewers' consensus score to establish a final total score up to 100 points.
- For the community review, each application will be assigned to two community reviewers. Before the committee meeting, the community reviewers will provide a written review, including a score (out of 100 points), for each application assigned to them with a major emphasis on the lay summary and benefits sections. These individual written reviews will be submitted to the remainder of the committee before the meeting.

Following the discussion between all the members of the scientific committee with the community reviewers providing additional comments/critique, the applications will be ranked by their final total scientific review scores (which includes the EDI score).

Subsequently, applications will be selected for funding, based on their ranking and the availability of funds, provided they have scored at least 70 points in both the scientific (including EDI) AND the community evaluation.

8. Timeline

Date	**Stage**
June 12, 2024	Competition launch
August 27, 2024, noon (EDT).	**Mandatory registration deadline: Please submit the registration form to** R-CFTR@genomequebec.com
Early September 2024	Notice of eligibility
October 16, 2024, noon (EDT).	**Application submission deadline: Please submit your application (including the budget and statement(s) of work for external services) to** R-CFTR@genomequebec.com
Mid-December 2024	Meeting of the evaluation committee
January 2025	Notice of award
April 1, 2025	**Start of the project**

Note: Génome Québec, in agreement with Cystic Fibrosis Canada, reserves the right to change the dates if necessary. Any changes made will be indicated on the competition's website.

9. Contact

For further information, please contact:

Annina Spilker, Program and Strategic Initiatives Manager, Scientific Affairs, Génome Québec
R-CFTR@genomequebec.com

Appendix I. Génome Québec financial guidelines

Génome Québec's financial guidelines will govern the management of funded projects and the use of funding: https://genomequebec.com/wp-content/uploads/2023/06/GENOME-QUEBEC-FINANCIAL-GUIDELINES_March2020.pdf

In addition, for this competition, the following rules apply and supersede the financial guidelines:

- Neither cofunding nor any other commitment from a User is required for this competition.
- Project expenses are eligible as of the date of the notice of award.
- The funds can't be used to buy an equipment exceeding the price of $25,000 and the sum of the equipment costs per project can't exceed 25% of the total budgeted eligible expenses.
- Whenever possible, equipment built in Québec, consumables distributed in Québec and services offered in Québec should be favoured.
- Scientific and financial reporting will follow an annual schedule.
- The receipt of all financial and scientific reports by Génome Québec (complete and compliant with deadlines) will be required to receive (timely) fund transfers during the project's lifecycle.
- Project changes (including changes related to science, finances, and team composition) must be approved and managed by Génome Québec, which will inform Cystic Fibrosis Canada, when applicable.

Appendix II. Guiding principles on equity, diversity and inclusion

https://genomequebec.com/wp-content/uploads/2024/06/EDI-guiding-principles.pdf

Appendix III. Evaluation criteria

Applications will be evaluated by a committee of independent scientific peer reviewers, EDI expertise and cystic fibrosis community reviewers to assess the scientific merit and effectiveness of the proposed plan to advance the objectives of this competition, considerations of equity, diversity and inclusion and consideration of the needs of people affected by cystic fibrosis, based on the criteria below (for details on the review process, see section 7).

The role of the community reviewers is to assess the potential impact of the project and, if the proposal involves the participation of people affected by cystic fibrosis, if their needs are taken into account. Since the lay summary and benefits section are used by the community reviewers to understand what the proposal is about, writing them at an inaccessible language level can impact the proposal review, up to its dismissal (see section 7). These sections should be written in non-scientific, everyday language at a level no greater than Grade 10. Please use a readability index such as the Hemingwayapp online tool to confirm the level. If this application is funded, the summary may also be used to communicate to the public and donors about the research supported by Cystic Fibrosis Canada and Génome Québec.

The descriptors following each criterion are not all-inclusive. The weight assigned to each scientific review criterion is shown in parentheses.

Community review criteria:

- Clarity and accessibility of the lay summary and benefits section.
- Clarity of the focus of the project and why it is important (rationale, objectives, design).
- Adequate and well described potential benefits/impact for people carrying rare mutations.
- Relevance and importance of the proposed project to the people affected and to the priorities of the cystic fibrosis community.
- Extent to which research aligns with the objectives of the call.

Scientific review criteria (including EDI):

I. Project (85 points)

Scientific merit of the research project (40 points)

- Application aligns with the objectives of the competition (see section 2).
- Use of *omics* tools to advance knowledge (applied genomics or related research areas such as proteomics, metabolomics, bioinformatics, genetic engineering, synthetic biology, and research intended to alter the function of one or several genes, etc.).
- Quality of proposed scientific activities.
- Extent to which the proposed strategies will contribute to the comprehension of the mechanisms underlying disease associated with rare mutations and/or to the development of new treatments.
- Clarity and pertinence of the deliverables, the critical path, objectives, and overall project goal.
- Presence of a reasonable data and resource management plan compliant with the Tri-Agency policies listed in section 3).

Project feasibility (25 points)

- Feasibility of the project, including, without being limited to, appropriate deliverables in a feasible timeline, appropriateness of the methodology and the timely access to data sets, samples or any other material required.
- Risk management.
- Reasonable and justified budget.

Benefits of the project (20 points)

- Justification of potential benefits which could be reasonably expected for people with rare CFTR mutations.
- Well defined knowledge dissemination strategy.

II. Team, training of the next generation, and EDI considerations (15 points)

Team and training of the next generation (10 points)

- Justification of the team composition, including but not limited to, multidisciplinary, relevance of researchers' expertise for the research to be conducted and integration of early-career researchers (professors who accepted their positions within the last five (5) years, postdoctoral fellows) into the team and training of students and postdoctoral fellows.

Considerations related to equity, inclusion, and diversity (5 points)

- Relevance of the activity or the activities proposed to address the EDI challenge(s) identified in the context of the proposed project.

For more information, please consult the EDI Guidelines under Appendix II.
This section will be evaluated by an EDI expert. Their evaluation will be based on the application as a whole and the activities or methods that the research team plans to use to uphold EDI principles.