IRCM MONTREAL CLINICAL RESEARCH INSTITUTE

2016-2021

STRATEGIC PLAN

TWO MAJOR INITIATIVES:

RESEARCH CENTRE ON RARE AND GENETIC DISEASES IN ADULTS

ESTABLISHMENT OF A PIPELINE FOR THE PRODUCTION OF BIOMARKERS INCLUDING DISCOVERY, VALIDATION, CLINICAL TRIALS AND THE DEVELOPMENT OF PARTNERSHIPS FOR COMMERCIALIZATION

OCTOBER 1, 2015

TABLE OF CONTENTS

IRCM (Institut de recherches cliniques de Montréal)
110 avenue des Pins Ouest, Montréal (QC) H2W 1R7
www.ircm.qc.ca

EXECUTIVE SUMMARY

IRCM management started a strategic planning exercise in fall 2014 focused on scientific development in order to ensure the institute's sustainability. A mobilization approach was conducted among laboratory directors during five meetings, which were followed by consultations with each research division and with the Scientific Advisory Board. The plan was then presented to the institute's and the Foundation's Board members. The final document was submitted to the IRCM Board of Directors on September 22, 2015.

The central component of the IRCM's 2016-2021 strategic plan is the establishment of **two major institutional initiatives**: I) a Research centre on rare and genetic diseases in adults, and II) a pipeline for the production of biomarkers including discovery, validation, clinical trials and the development of partnerships for commercialization.

Initiative I: Research centre on rare and genetic diseases in adults

Why rare diseases?

- A field in great expansion at the international level in both the public and private sectors
- Canada is at the forefront of research in this field
- The governments of Canada and Quebec greatly support this field
- Very large gap in the healthcare system for patients with rare diseases who reach adulthood

Why the IRCM?

- A large number of IRCM researchers conduct research involving various rare diseases
- The IRCM clinic is extremely well-positioned to develop a model of transitional care for patients leaving pediatric hospitals for adult hospitals
- The IRCM already works in this unique niche with cystic fibrosis and rare immunodeficiencies

Key components to finalize or implement:

- Partnership with CHU Sainte-Justine to ensure the transition of care
- Partnership with CHUM specifically for rare diseases
- Partnership with the Regroupement québécois des maladies orphelines
- Obtain support from the Faculty of Medicine at the Université de Montréal to train the next generation of experts
- Obtain a development budget from the government of Quebec to directly support the institute's two major initiatives: $3 million over five years ($600,000 per year starting in 2016-2017, including $1.4 million allocated to Initiative I)
- Obtain support from the Quebec Ministry of Health and Social Services (ministère de la Santé et des Services sociaux) (MSSS)
- Recruit two researchers in the field of rare diseases and translational research

Initiative II: Pipeline for the production of biomarkers

Why a biomarkers pipeline?

- A field in great expansion at the international level in both the public and private sectors
- Companion diagnostics are a key element of personalized medicine (or precision medicine)
- Biopharmaceutical companies are very interested in biomarkers
- No biomarkers pipeline model has been established in Canada

Why the IRCM?

- A large number of IRCM researchers conduct research involving the discovery of biomarkers
- The IRCM houses state-of-the-art technological platforms for biomarkers, including quantitative clinical proteomics
- The IRCM can recruit patient cohorts through its clinic for the validation of biomarkers
- The IRCM already works in this niche, namely with the development of drugs targeting PCSK9 for the treatment of bad cholesterol

Key components to implement:

- The pipeline's operational structure based on a public/private consortium
- Establishment of a steering committee
- Recruitment of a pipeline project manager
- Obtain support from the Quebec Ministry of Economy, Innovation and Exports (ministère de l'Économie, de l'Innovation et des Exportations) (MEIE)

Implementation and funding

Implementing these two initiatives requires $11 million in funding over five years.

Financial support:

- The IRCM Foundation
- The IRCM, through its operating budget (salary for researchers and personnel already participating in the initiatives)
- The Canada Foundation for Innovation (CFI)
- The pharmaceutical or biotechnology industry (for instance, Caprion)
- A development budget from the government of Quebec intended directly for the institute's two major initiatives, including $1.6 million for Initiative II

Implementation:

- Supervision of the implementation plan: Dr. Tarik Möröy, IRCM President and Scientific Director, and Dr. Pierre Chartrand, Director of strategic partnerships at the IRCM.

INITIATIVE I

Research centre on rare and genetic diseases in adults

Drawing on its exceptional strengths in clinical and basic research, the IRCM launched a major institutional initiative aimed at establishing the Research centre on rare and genetic diseases in adults. The centre will be the only one of its kind in Canada and will fill a substantial void in this area regarding the management, monitoring and care of adult patients with rare diseases.

Today, as major achievements in biomedical research result in better treatments, a growing number of patients with rare diseases reach adulthood. However, our healthcare system has no specific intake services for these patients. Moreover, very little is known about the impact that reaching adulthood has on disease progression and, consequently, on treatment. Pediatricians, patient associations and the MSSS all recognize the importance of setting up clinics for patients with rare diseases who must leave the pediatric environment.

The IRCM's initiative will not only provide access to specialized care, but will also become a key component of the translational research program required to better understand these diseases and develop new, innovative treatments. The IRCM has begun forming three important partnerships to support this initiative. The first partnership is with the CHU Sainte-Justine university health centre, the largest research and treatment centre in Quebec for rare diseases in children. The second partner is the Centre hospitalier de l'Université de Montréal (CHUM), which will be an essential partner for the implementation of patient care and treatment in the Quebec hospital sector. Lastly, the third partner is the Quebec Coalition for Orphan Diseases (Regroupement québécois des maladies orphelines, RQMO), whose mission is to inform and support patients with rare diseases over the course of their lives, raise public and government awareness, and advance research in this area.

This new initiative constitutes the next logical step for the institute's clinical activities, which currently focus on studying and treating complex cardiometabolic disorders and diseases associated with lipid metabolism (many of which are rare diseases), as well as for its major basic research programs in immunology, neuroscience and human genetics.

Required investment: $7.7 million for five years
The IRCM will contribute $2.5 million from its operating budget to this new centre. The IRCM Foundation will contribute an additional $1.9 million, and $1.4 million would provide from part of a new development budget given to the IRCM by the MEIE ($1.4 million out of $3 million). Lastly, $800,000 will be invested from grants obtained by the researchers responsible for this project. Another $1 million, needed for the research infrastructure of two new laboratories (laboratory and major equipment), will be funded by the IRCM's budget associated with the CFI's Leaders Fund program.

Anticipated benefits for Quebec
The current costs of healthcare for adult patients with rare diseases are substantial, due in large part to a lack of appropriate patient care and inadequate treatments. The centre proposed by the IRCM will significantly contribute to reducing these costs. In addition to net benefits for Quebec patients with rare disease and job creation, the federal grants given to researchers participating in this initiative will represent at least $500,000 per year (typically, at the IRCM, one dollar is obtained from the federal government for every dollar invested by the government of Quebec).
Total: $1.4 million over five years

Purpose and justification

Why take on this project and establish this new research centre?
A disease is deemed rare when it affects less than one person in 2,000. While the diseases may be rare, the patients are not, as approximately 8,000 rare diseases exist. Therefore, in total, 2.5 million Canadians are affected, including more than 500,000 people in Quebec. Only a few of these diseases can be treated effectively, so rare diseases represent a significant public health concern, especially now that a growing number of patients with rare diseases reach adulthood. The Quebec health care system is compartmentalized into pediatric and adult health care services, and no specialized service currently exists for adult patients with rare diseases. As a result, they do not receive the necessary management, care, and high-quality follow-up. Moreover, very little is known about the impact of reaching adulthood on disease progression and treatment. Consequently, the IRCM's initiative addresses a significant concern regarding the management and care of patients with rare diseases within the adult healthcare system.

What needs are addressed by this initiative?
The IRCM's proposed Research centre on rare and genetic diseases in adults addresses an urgent need in Quebec and Canada. The new centre will allow the institute not only to conduct research on these diseases, but also to develop a model for clinical follow-up, which does not currently exist in Quebec and Canada, to ensure the transition of care for patients who reach adulthood and must leave the pediatric environment. By following the progress of adult patients with rare diseases, the IRCM will establish a model that will make it possible to better define the progression of these diseases and discover the cellular and molecular causes for this progression, with a view to improving treatment. The model will therefore allow the IRCM to position itself as a national leader and will result in the implementation of similar centres throughout Quebec and Canada.

Research is an essential component of this program, as many of the diseases involved are orphan diseases, that is to say they are rare and no treatment options exist. In addition to providing access to specialized care, the IRCM's new centre will develop a much-needed translational research program to better understand these diseases and ultimately develop new treatments. These studies will greatly benefit from the contribution of the IRCM's basic researchers, who are recognized worldwide for their work on the molecular mechanisms of diseases (see Appendix, Table 1).

Why is the IRCM well suited to the task?
The IRCM is well known for its excellent basic biomedical research and its mission to understand the causes of diseases. With its recognized expertise in immunology, developmental neurobiology, and cardiovascular and metabolic diseases, the IRCM is perfectly positioned to create a centre of excellence in clinical research on rare and genetic diseases associated with these fields. Moreover, the IRCM houses an outpatient clinic that receives more than 12,000 patient visits each year and conducts several research projects on certain rare diseases. In addition, the clinic is already treating adult patients with cystic fibrosis and hyperlipidemia, which are rare diseases.

At the IRCM, research is supported by ultramodern core facilities, 35 research units led by well-renowned principal investigators, 130 graduate students (Master's and PhD), approximately 60 postdoctoral fellows and a cohort of over 200 employees – all entirely dedicated to research. The IRCM clinic has more than 25 clinicians, as well as a team of 17 health professionals, including nurses, nutritionists and kinesiologists.

The IRCM is therefore in an excellent position to create the Research centre on rare and genetic diseases in adults.

What is the IRCM's strategy?
The IRCM is proposing to establish on its premises a research centre entirely dedicated to researching rare and genetic diseases in adults. The centre will assess and monitor adult patients with rare diseases such as primary immunodeficiencies (which are often caused by hereditary or genetic defects) and certain cardiometabolic diseases, including cystic fibrosis (which is also hereditary and caused by a genetic mutation). Clinicians working at the IRCM and affiliated with the CHUM, such as Dr. Hugo Chapdelaine and Dr. Yves Berthiaume, will meet with patients. A clinical researcher and a human genetics researcher (see below) will oversee the clinical and translational research activities involving these patients. They will also regularly work with the IRCM's basic researchers, who will help them better understand rare diseases at a molecular level and find new treatments for these diseases.

Two of the IRCM's most experienced researchers will co-direct the centre: Dr. André Veillette, who will represent basic research, and Dr. Yves Berthiaume, who will represent clinical research and clinical activities. These researchers are world-renowned experts in immunology and rare pulmonary diseases, respectively.

The co-directors will be supported by the IRCM's existing teams of basic researchers who have expertise in rare and genetic diseases (see Appendix, Table 1). Furthermore, the centre will recruit a new, distinguished clinical researcher specializing in immune diseases, in particular primary immunodeficiencies, which will consolidate the IRCM's expertise in immunology, as well as a human genetics researcher, who will provide the IRCM with specialized research expertise in discovering and analyzing the inherited mutations of rare diseases.

All of the centre's teams will work in close collaboration to ensure that discoveries make their way from the patient's bedside to the basic research laboratory, and vice-versa.

Which resources does the IRCM already possess and which are needed?
Nearly half of the IRCM's basic researchers are already studying rare diseases. Dr. Yves Berthiaume is also installed at the IRCM and ready to launch the clinic for adult patients with cystic fibrosis. Furthermore, the IRCM is currently in negotiations with CHUM clinicians to start a primary immunodeficiencies clinic. As mentioned above, the IRCM will recruit two new clinical researchers —one specializing in primary immunodeficiencies and the other in human genetics— to round out the team.

Who will be the centre's partners?
To successfully complete this project, the IRCM's management team is finalizing three strategic partnerships. Negotiations are underway with the first partner, the CHU Sainte-Justine, which is the largest research and treatment centre in Quebec for rare diseases in children. Due to its mandate, this hospital can only treat patients until the age of 18. A partnership will ensure these patients are transferred to the adult hospital environment. Collaborations already exist between IRCM and CHU Sainte-Justine researchers, and this project will make it possible to establish a more formal framework for joint research activities, as well as harmonize follow-up for patients with rare diseases who reach adulthood. The second partnership is with the CHUM, which is already an IRCM partner for the emergency clinical follow-up of patients seen at the IRCM clinic and for cases requiring hospitalization or interventions not available at the IRCM. As the CHUM is a hospital for adults, it will also be able to perform these functions for adult patients with rare diseases seen at the IRCM's Research centre on rare and genetic diseases in adults. Lastly, the IRCM recently signed a partnership agreement with the Quebec coalition for orphan diseases (Regroupement québécois des maladies orphelines, RQMO), a provincial organization that represents the interests of patients with rare diseases in Quebec (see additional information in the appendix). This new strategic partnership will allow the IRCM's health professionals and researchers to refer their patients or participants in their research projects to the Centre d'information et de ressources en maladies rares, which is an information and resource centre on rare diseases managed by the RQMO. The IRCM and the RQMO also plan to develop common projects in rare disease awareness, education and research. As part of the agreement, the RQMO moved its offices to the ground floor of the IRCM in September 2015.

The research centre

Structure and governance
The new centre will be located at the IRCM and co-directed by Dr. André Veillette and Dr. Yves Berthiaume. Dr. Veillette is a Full IRCM Research Professor and Director of an immunology research unit at the IRCM. He will be responsible for developing the centre's basic research, particularly in the area of primary immunodeficiencies. Dr. Yves Berthiaume, Full IRCM Research Professor and Director of a cystic fibrosis research unit, will develop the centre's clinical research, predominantly in regards to pulmonary diseases and human genetics. The co-directors will invite teams from each IRCM research division to work with the centre, among the researchers interested in rare diseases within their own fields. They will also recruit two new researchers who specialize in primary immunodeficiency diseases and human genetics. The centre will be equipped with new infrastructure subsidized by the CFI and staffed with nurses, research associates, technicians and a bioinformatics scientist.

The IRCM will make its clinic's spaces and laboratories available to the centre and will ensure its researchers have unlimited access to the institute's core facilities, animal facilities and related services.

Dr. Tarik Möröy, IRCM President and Scientific Director, will be in charge of scientific supervision and the centre's implementation plan. Dr. Pierre Chartrand, Director of strategic partnerships at the IRCM, will oversee partnership development. The IRCM's finance department will manage the centre's finances, as is the case for all IRCM projects and grants. After an initial five-year period, the centre will be evaluated based on pre-established performance criteria, namely quality of care, development of new therapies and diagnostic tools, impact on the management of patients with rare diseases, treatment progress and patient quality of life.

The centre's research program: basic and translational research

This component will be led and supervised by Dr. André Veillette, a world-renowned expert in immunology. He has characterized several molecules that are associated with the development of certain immunodeficiencies and represent potential targets for therapeutic immunosuppression to treat autoimmune diseases and transplant rejections. Dr. Veillette will develop a research program on rare and genetic immunodeficiency diseases in adults. These primary immunodeficiency diseases are rare and generally inherited forms of immunodeficiency, and include such diseases as X-linked agammaglobulinemia (XLA), severe combined immunologic deficiency (SCID), X-linked lymphoproliferative disease (XLP) and common variable immunodeficiencies (CVID). Patients with these diseases are more likely to develop serious infections that can lead to death, as well as certain types of cancer such as lymphoma. These diseases are generally diagnosed in children, but more and more cases are now detected and diagnosed in adults. Furthermore, with such therapeutic advances as hematopoietic stem cell transplantation, intravenous immunoglobulin and effective anti-microbial agents, children with primary immunodeficiencies often survive until adulthood, at which time they often develop new problems or complications stemming from their disease or past treatments.

Implementation and recruitment

To establish this research program, Dr. Veillette will dedicate a significant portion of his laboratory's research time to projects involving rare diseases that affect the immune system. He will collaborate with IRCM teams working in immunology and rare diseases. In collaboration with the IRCM's management team, he will also recruit a clinical researcher who is an expert in primary immunodeficiencies as a laboratory director and research professor. This clinical researcher will have the dual responsibility of taking part in immunodeficiency-related clinical activities, by treating and following the progress of patients with these diseases, as well as ensuring the cohort of patients followed at the clinic participate as much as possible in clinical and translational research projects aimed at better understanding their diseases and developing new treatments. He will also manage his own laboratory, where he will conduct basic and translational research, thereby acting as the bridge between the clinic, clinical research, basic research and translational research on primary immunodeficiencies at the IRCM. He will thus complement the work on these diseases carried out by Dr. Veillette and other basic researchers at the IRCM.

The centre's research program: clinical research

This component will be led and supervised by Dr. Yves Berthiaume, who is also Executive Director of the clinic and clinical research at the IRCM. Dr. Berthiaume is an expert recognized worldwide for his work on cystic fibrosis (CF), a genetic pulmonary disease that is a paradigmatic example of the purpose of a program for rare and genetic diseases in adults. Indeed, thanks to advances in research, people with CF are living longer than ever. However, improved life expectancy leads to metabolic disorders such as diabetes for adults with CF. This form of diabetes is different than type I or type II diabetes and is not found in children with CF, which perfectly illustrates the need for a research program on rare diseases in adults. Furthermore, Dr. Berthiaume will develop research projects focused on the interaction between the inflammatory response and epithelial dysfunction in pulmonary pathologies. This aspect connects with Dr. Veillette's work on diseases affecting the immune system. Dr. Berthiaume will also develop a research program aimed at identifying new biomarkers that characterize the development of metabolic problems in adults with cystic fibrosis.

Implementation and recruitment

To establish this research program, Dr. Berthiaume will dedicate a significant portion of his laboratory's research time to projects involving rare pulmonary diseases. He will collaborate with IRCM teams that work in this field and other areas relevant to rare diseases. Lastly, with the IRCM's management team, he will recruit a researcher specializing in human genetics, who will become a laboratory director and research professor and will be an expert in the human genetics of rare diseases in adults. Recruiting a human genetics expert is crucial for the centre, and the researcher will have to specialize in the study of genetic variations associated with rare diseases. His or her research will include the following:

- Analyzing the determinants responsible for the specific inherited traits associated with a rare disease, resistance to such diseases and the progression of such diseases in adults.
- Understanding the relationship between the variations or mutations and the pathophysiology of each disease studied, as well as the differences between the pathogenesis in children and adults.
- Developing methods to establish animal and cellular models, including human stem cells, for the studied diseases.
- Managing human samples and administrative support for human genetics.
- Analyzing data generated by high-throughput screening, as well as bioinformatics analysis and management.

The centre's innovative and unique features

A reference centre for adult patients with rare diseases

Under Dr. Yves Berthiaume's supervision, the IRCM's clinicians will provide ambulatory care to patients previously monitored by such pediatric hospitals as the CHU Sainte-Justine. New adult patients with rare diseases, or those suspected of suffering from a rare disease, will also be evaluated. The IRCM estimates that 500 to 1,000 patients will be monitored at the clinic, in collaboration with the CHUM's Department of Medicine.

New diagnostic tools

The new human genetics researcher will be responsible for establishing the genetic cause of new rare disease cases identified with modern diagnostic tools, including whole-exome sequencing performed by the IRCM's functional genomics core facility.

An innovative research program

This innovative program, which will include the evaluation of new treatments for outpatients, will be established under Dr. Yves Berthiaume's supervision. Research with cohorts of adult patients with rare diseases will be conducted in collaboration with IRCM researchers, in the institute's areas of expertise including pulmonary diseases, rare hyperlipidemia and cystic fibrosis-related diabetes, as well as the field in which the new clinical researcher in primary immunodeficiencies will be working. This research will make it possible to better understand how the genetic mutations that cause rare diseases lead to specific pathologies in adults. This knowledge will then enable the creation of new monitoring and research models, to the benefit of adult patients with rare diseases.

Internal commitment

Many IRCM researchers are already studying the molecular mechanisms of certain rare diseases. An internal grant program of $100,000 per year will be established to encourage the development of new translational research programs on rare diseases.

Better training for the next generation of researchers

Under the supervision of Drs. Yves Berthiaume and André Veillette, the new centre will train future generations of clinicians, clinical researchers, nurses and other health professionals, as well as basic researchers specialized in rare diseases in adults and scientists interested in better understanding the specific pathogenic mechanisms in adults and developing new treatments for these diseases.

Databases and indexes of rare and genetic diseases in adults

The new human genetics researcher will be responsible for systematically collecting data and blood samples from adult patients with rare diseases. These samples will be available for future research aimed at better understanding the mechanisms of these diseases and their progression in adults.

INITIATIVE II

A pipeline for the production of biomarkers including discovery, validation, clinical trials and the development of partnerships for commercialization

The IRCM intends to become the academic leader in the creation of a public-private consortium aimed at the discovery, development and clinical validation of a pipeline of biomarkers that will be used for diagnosis and to develop new drugs in preventive medicine. The consortium's natural partners are already moving in the same direction: Montréal InVivo, MEDTEQ (Quebec Consortium for Industrial Research and Innovation in Medical Technology) and CQDM (Quebec consortium for drug discovery). The Quebec Network for Personalized Health Care (QNPHC) also reacted favourably to the IRCM's initiative. In addition, Caprion, a well-established biopharmaceutical firm in Montréal, confirmed its support and intention to form a partnership with the institute (see page 14).

Required investment: $3.5 million for five years
This funding will be provided through the sum of $1.6 million from the second part of a $3-million development budget from MEIE, an in-kind budget of $900,000 from an industry partner (Caprion), and the sum of $500,000 stemming from the activities of a new biomarker laboratory. In addition, $500,000 for the biomarker laboratory's research infrastructure will come from the IRCM's budget associated with the CFI's Leaders Fund program.

Anticipated benefits for Quebec
Other than direct revenues from the biomarker laboratory (estimated at $500,000 for the five-year period), benefits include stimulating Quebec's R&D, generating savings associated with precision medicine, and improving patients' health and life expectancy. Biomarkers will enable early detection of disease and improved diagnosis, which in turn, will lead to prevention and a reduction in waste associated with multiple diagnoses. With this technology, it will also be possible to evaluate patients' responses to drugs, which will lead to improved patient stratification and, as a result, to fewer prescriptions and a better use of drugs. In addition to these medium- or long-term economic benefits, the consortium should be able to attract, in the short term (after the start-up period), approximately one dollar from private sources (pharmaceutical companies, philanthropic foundations) and the federal government for every dollar invested by the government of Quebec.
Total: $1.6 million over five years

Purpose and justification

The field of biomarkers is in great expansion on an international level, in both the public and private sectors, and the role of these biomarkers in companion diagnostics has become a key component of personalized (or precision) medicine. Biopharmaceutical companies are very interested in biomarkers, but the process of development, validation, certification and commercialization remains under developed. In addition, large pharmaceutical companies are leaving this development up to research institutions and biotechnology companies.

The model proposed by the IRCM for the biomarkers pipeline does not currently exist in Canada and could remedy this situation. The IRCM is well-positioned to develop this pipeline model for several reasons:

- Several research projects involving the discovery of biomarkers are already being conducted.
- The IRCM houses state-of-the-art technological platforms that are required for the development of biomarkers, including quantitative clinical proteomics.
- Thanks to its clinical research installations, the IRCM can recruit patient cohorts for the validation of biomarker candidates.
- The IRCM already works in this niche, namely with the development of drugs targeting PCSK9 as well as other genes that predispose patients to rare diseases (like GFI1).

Implementation

Governance

This project will be the work of a public/private consortium that will bring together the IRCM from the academic sector with private partners (like Caprion) and pharmaceutical companies (discussions underway), who will jointly set up a steering committee.

Implementation

To accelerate the discovery and validation of high-impact biomarkers, the consortium needs to establish a biomarkers pipeline similar to a pharmaceutical pipeline for drug discovery. The key component of this process is a steering committee made up of scientific, clinical, technological and commercialization experts, whose task is ensuring the pipeline is operational and has targeted impact. This process is established through a series of orchestrated measures, each with a “go/no-go” decision type:

- Screening each biomarker candidate using a scouting process from among IRCM teams’ research projects.
- Launch of a rigorous evaluation process in regards to:
  - The potential impact of the biomarker candidate on the development of diagnostic, prognostic and therapeutic tools for diseases of interest, while taking into account existing biomarkers in the field.
  - Access, through the IRCM clinic or partnerships, to necessary patient cohorts and the biological material required for validation.
  - The potential for developing an effective clinical test: quantitative clinical proteomics, epigenetics and clinical genomics (specificity, sensitivity, reproducibility).
  - The potential for the commercial development of a cost-effective clinical test.
  - Interest of biopharmaceutical partners in commercialization.

For each selected biomarker candidate, the IRCM will ensure the availability of financial resources and scientific or technological expertise, either through its internal community or its partners. From the start, relevant biopharmaceutical partners will participate in the development process for selected biomarkers to ensure they meet commercialization requirements.

An example of a very promising biomarker being developed at the IRCM is PCSK9, a proprotein convertase discovered at the institute by Dr. Nabil G. Seidah. PCSK9 is involved in a number of diseases associated with cholesterol metabolism, such as atherosclerosis, diabetes and obesity and, potentially, to various heart conditions. The IRCM also developed a new PCSK9-dosing technology through semi-automatic mass spectrometry that showed a novel link between soluble PCSK9 circulating in the bloodstream and metabolic phenotypes from patient cohorts. PCSK9 is a biomarker candidate currently in an active development phase with IRCM partners (Fondation Leducq in Europe, Sanofi-Regeneron and ThermoFisher).

Several other biomarkers are currently being studied at the IRCM, such as the transcription factor gene and epigenetic modifier GFI1 (*Growth factor independence 1*). A genetic variant of GFI1 was discovered in 2010 by an IRCM researcher and it has since been found that this variant is associated with a high risk of developing acute myeloid leukemia (AML), either *de novo* or following a myelodysplastic syndrome (MDS), which precedes AML. The presence of this variant can be used to estimate the risk for a patient with MDS of developing AML, but can also be used to choose the best therapeutic strategy, which could become a new tool for personalized medicine.

Caprion's positioning with respect to this initiative (text provided by Caprion, translated)

Mass spectrometry and biomarkers: need and unique opportunity in Quebec
Personalized medicine is an opportunity to provide patients with real benefits and reduce costs for the healthcare system. Multiple applications are already providing significant benefits for patients, particularly in the field of cancer, by making it possible to select the best treatment for each patient. The success of this approach is based on the development of effective biomarkers to accurately diagnose diseases, predict the progression of the pathology, select the best drug for each patient or monitor therapeutic response. Discoveries made in recent years have also demonstrated the benefits of combining biomarkers into a single panel to increase the algorithms' diagnostic performance. These methods are well established on a genomic level and, recently, technological breakthroughs have led to panels of biomarkers on a proteomic level.

A new mass spectrometry approach has emerged in recent years as the choice technology for the development of diagnostics focused on proteomic panels. This platform is called *multiple reaction monitoring* (MRM). Four key benefits set this platform apart and support its adoption:

1) An ability to multiplex the quantitative measurement of several hundred proteins into one single and quick test adapted to large-scale deployment.
2) The absence of the use of antibodies, allowing for rapid and inexpensive development.
3) A specificity surpassing that obtained by immunodetection technologies.
4) The availability of high-performance MRM instruments certified "Class 1 Medical Device" that can be installed in a medical service laboratory environment and support tests approved by regulatory agencies (tests 510k and PMA, for instance).

The recent commercialization of diagnostic tests based on the use of mass spectrometry by Integrated Diagnostics, Sera Prognostics, Biodesix and Quest Diagnostics has demonstrated the performance of the technological platform, as well as the relevance of the scientific approach and commercial potential.

An innovative, structuring and strategic initiative for personalized medicine in Quebec

The proposed initiative is a strategic one for the discovery and development of new diagnostic tools based on protein biomarkers, as it is built around a strategic partnership between the IRCM and Caprion. This initiative will use MRM technology to position and accelerate the development of diagnostic solutions. This initiative's differentiating factors are based on three pillars originating for the unique combination of expertise found at the IRCM and Caprion.

A central laboratory serving the healthcare system

Due to its leadership role in the Personalized Medicine Partnership for Cancer (PMPC), Caprion is already well underway in establishing a central laboratory for the commercial development of diagnostic tests based on the use of MRM, namely in oncology. This platform will therefore be available for the development and commercialization of innovative diagnostic tests resulting from the IRCM's research. Together with IRCM researchers, Caprion will leverage its expertise to develop, validate and commercialize MRM tests that fulfil unmet medical needs. The participation of IRCM clinical researchers will also provide access to patient cohorts required for the verification and validation of diagnostic tests, which is an important advantage of this partnership. Considering that 80 per cent of diagnostic tests are currently based on generally inefficient individual protein measures (such as PSA, CA125 or CEA), this initiative intends to develop multiplexed tests to simultaneously measure several proteins, which will have a direct impact on the tests' performance and costs for the healthcare system.

Technological development

The combined expertise in mass spectrometry of IRCM researchers and Caprion scientists offers a unique opportunity to further the development of mass spectrometry applications, especially in order to improve the robustness, sensitivity and output of the developed tests within the framework of an accredited medical laboratory offering consolidated services to Quebec hospitals.

Pipeline for the development of innovative biomarkers

In addition to advanced technological expertise, the discovery of innovative biomarkers requires a deep clinical and pathological knowledge of the targeted pathologies, as well as access to patient cohorts for the discovery, verification and validation of the biomarkers. In this respect, the IRCM-Caprion partnership will benefit from the contribution of clinical and basic researchers to develop accurate diagnostic applications that fulfil unmet needs and have a well-defined clinical purpose. From the design stage of the diagnostic applications, IRCM researchers will provide necessary leadership to ensure the applications' relevance within specific clinical contexts. The researchers will also contribute to drafting the strategy for technological development. Close collaboration between the IRCM and its commercial partner Caprion from the initial stages will ensure the technological development is consistent with the commercial development, particularly through the consolidation of standardized procedures with the appropriate regulatory aspects, which are mastered at Caprion.

Benefits

The proposed initiative will provide Quebec patients access to innovative and efficient diagnostic solutions that fulfil unmet medical needs, thus providing better therapeutic choices optimized for each patient and offering savings for the healthcare system. Moreover, commercialized diagnostic solutions will be marketed internationally, thereby leading to significant economic and tax benefits. In this respect, due to its commercial activities in the field of biomarkers and diagnostic development, Caprion provides an immediate marketing outlet and a wide reach for the developed expertise and intellectual property. This initiative will consolidate Quebec's leading expertise in the diagnostic field and contribute to increasing Quebec's leadership in personalized health, both nationally and internationally.

FINANCIAL REQUIREMENTS

Research centre on rare and genetic diseases in adults:

- Salary support for the centre's two co-directors, Dr. André Veillette and Dr. Yves Berthiaume, as well as for their research associates
- Recruitment of a clinical researcher specializing in human immunodeficiencies
- Recruitment of a researcher specializing in human genetics
- Funds to support these two new researchers: salary support, start-up funds, staff and infrastructure funds
- Operating funds for the new rare and genetic disease clinic, staff, infrastructure
- Operating funds to cover indirect costs

Biomarkers pipeline:

- Salary support for the pipeline's project manager
- Development of the protein micro-network technology to round out the proteomics platform
- Salary support for the bioinformatics expert to develop and install the bioinformatics database, develop software for data modelling, create the database, compare gene and protein expression data, predict the structure of and manage large datasets
- Salary support for the staff managing the biobank in order to establish well-documented collections of human samples for clinical proteomics, epigenetics and genomics
- High-quality and well-characterized standard reagents that can improve the specificity and reproducibility of technologies in proteomics, epigenetics and genomics
- Support for equipment and maintenance costs
- Operating funds to launch the project
- Access to clinical research staff to manage patient cohorts and gather data and samples

APPENDIX

Table 1: List of IRCM researchers studying rare diseases

Dr. Marlene Oeffinger Fryns Syndrome Shwachman-Diamond syndrome	**Dr. Marie Trudel** Sickle cell disease Thalassemia Polycystic kidney disease
Dr. William Y. Tsang Ciliopathies	**Dr. Tarik Möröy** Inherited bleeding disorders
Dr. Jean Vacher Osteopetrosis	**Dr. Yves Berthiaume** Cystic fibrosis
Dr. Yves Berthiaume/ Dr. Rémi Rabasa-Lhoret Biomarkers of cystic-fibrosis-related diabetes	**Dr. Benoit Coulombe** Leukodystrophies Inclusion body myopathy Amyotrophic lateral sclerosis
Dr Michel Cayouette Stargardt disease Retinitis pigmentosa Leber's congenital amaurosis Macular degeneration	**Dr. Frédéric Charron** Gorlin syndrome Holoprosencephaly Familial congenital mirror movements Medulloblastoma
Dr. Jacques Drouin Cushing's syndrome	**Dr. Jean Davignon / Dr. Robert Dufour** Hereditary ichthyosis Familial hypercholesterolemia LCAT deficiency
Dr. André Veillette X-linked immunodeficiencies Scott syndrome Immunodeficiencies linked to Lck or ZAP-70 mutations	**Dr. Javier M. Di Noia** Immunodeficiencies linked to AID mutations

APPENDIX

The Quebec Coalition for Orphan Diseases (Regroupement québécois des maladies orphelines, RQMO)

The RQMO is unique in Quebec. Although associations directly related to specific rare diseases exist, the RQMO's goal is to build a unique coalition that represents all of them, especially those with a very small number of patients and for which it is difficult to make their voices heard. Certain better-known rare diseases, such as cystic fibrosis and muscular dystrophy, also have their own associations. In Canada, the closest equivalent to the RQMO would be CORD (Canadian organization for rare disorders, www.raredisorders.ca). However, this organization does not provide support or information services, making the RQMO unique in Canada. The RQMO thus provides information and support to all patients affected by a rare disease, as well as to their caregivers and health professionals.

- The RQMO has a full-time genetic consultant to provide official, factual and up-to-date information, called disease information sheets. This bilingual service is registered with Info Santé and other official registries.
- For genetic conditions, the RQMO can provide basic genetic counselling and request a consultation for genetic services when necessary.
- The RQMO refers people to community or government resources within the health care system.
- The RQMO is the Quebec representative of the project Orphanet-Québec, which is an international web directory of resources and activities related to rare diseases (www.orpha.net).
- The RQMO keeps the following directories updated:
    - Rare disease associations in Quebec and Canada
    - Relevant medical, government and community resources for people with rare diseases.

IRCM health professionals will have access to a search service for information and resources, which they will be able to use for the benefit of their patients and research projects. The IRCM will also have the possibility of pairing its patients with patients from the RQMO database. Other collaborations will also be possible, such as raising awareness of rare diseases or offering training on available resources in Quebec, as well as patient associations and their research projects. In return, the RQMO will benefit from being able to consult IRCM doctors, researchers and other healthcare professionals for complex requests and to provide guidance for undiagnosed patients. The RQMO can also participate in educational activities, professional development and the IRCM's research. The partnership between the IRCM and the RQMO will bring added value to the centre's reputation, as well as better access to medical, community and government resources and information for patients with rare and genetic diseases.