



## BACKGROUND

### 2017 Disruptive Innovation in Genomics Competition For Phase 1 Projects Advancing to Phase 2

Seven projects have been selected for funding under the 2017 Disruptive Innovation in Genomics Competition, to advance from Phase 1 of the program (this phase supports ideas for potential disruptive innovations) to Phase 2 (this phase supports the development of a prototype to advance the idea.) The total project budget is approx. \$19 million, which includes funding of approx. \$6.2 million from Genome Canada and the balance from co-funding partners.

#### **RapidAIM: A technology to rapidly assess the effects of compounds on individual microbiomes**

**Project leaders:** Daniel Figeys, Alain Stintzi, University of Ottawa

**Genome Centre:** Ontario Genomics

**Total funding:** \$2.9 million

Human microbiomes – the microbial colonies that exist in our guts –play a key role in disease development, progression, and therapeutic response. While global changes in the microbiome have been correlated to a disease or response to therapies, we lack methods to rapidly assess the impact of drugs and compounds on individual microbiomes. The development of a rapid screening platform would provide a groundbreaking and effective tool to screen novel and existing drugs and compounds for their effect on individual microbiomes. This would allow the screening of compounds for drug development to induce the desired changes in the microbiome.

Dr. Daniel Figeys and his team, in the first phase of this competition, demonstrated the proof-of-principle of RapidAIM, an assay that measures functional changes in individual microbiomes following exposure to drugs or compounds. The team is currently developing commercial applications, which include a fully automated, high-throughput prototype of the RapidAIM platform, together with a bioinformatics analysis platform, MetaLab. The Companion software developed for RapidAIM, META<sup>MCI</sup>, will rapidly assess the effects of drugs/compounds in individual microbiomes. The team will also create a drug-microbiome interaction database of

FDA approved and novel compounds to test RapidAIM and META<sup>MCI</sup>, in collaboration with their industrial partners Biotagenics and Filament BioSolutions.

The development and commercialization of RapidAIM will provide significant economic benefit. The product will enable identification of new drugs/compounds that target the microbiome, facilitate more rapid clinical development of drug candidates, prevent unwanted negative effects on the microbiome of new therapeutics, and achieve a better understanding of the impact of currently used therapeutics on the microbiome. The technology can also be used to select the most effective treatment for individuals, based on their microbiome's differing responses to drugs, improving health and reducing healthcare costs by targeting treatments to those who will benefit most.

### **AbSyn Technology for Identification of Synergistic Cancer Targets**

**Project leaders:** Jason Moffat, Charles Boone, University of Toronto

**Genome Centre:** Ontario Genomics

**Total funding:** \$2.7 million

Diagnosing disease has been revolutionized by our ability to decipher the genetic changes that lead to cancer; our treatment abilities have not kept up and most patients still receive decades-old treatments that do not target the individual genetic nuances of each individual's tumour and are highly toxic as well. The development of antibody-based drugs, such as Herceptin for breast cancer and Humira for rheumatoid arthritis, has changed the treatment landscape and had a tremendous impact on patient survival in these areas. But the success of antibodies is limited by our lack of ability to develop and apply efficacious new antibodies to kill target cells, particularly because of the complexity of diseases such as cancer.

Drs. Jason Moffat and Charles Boone of the University of Toronto's Donnelly Centre for Cellular and Biomolecular Research, with previous funding from Genome Canada, have invented AbSyn, a disruptive technology that combines expertise in the production of antibodies (Ab) and the deciphering of genetic networks to produce combination or synergistic (Syn) treatments for cancer. In the first phase of this competition, the researchers confirmed AbSyn's potential to be a robust drug discovery pipeline. Now, in phase 2, their goal is to promote the development of AbSyn into a platform that is attractive to the pharmaceutical industry. With the support of Celgene, a global leader in biopharmaceuticals, they will undertake large-scale screening to further demonstrate AbSyn's potential. The technology will ultimately be incorporated into Bridge Genomics, a Canadian start-up company, where it will enhance their mission of searching for disease-specific interactions that can be targets for drug development.

AbSyn presents an opportunity for Canada to attract the biotechnology investment needed to create a vibrant biotech sector in Ontario and attract and retain talented, highly trained researchers and have far-reaching economic benefits in terms of intellectual property and revenues. It will also highlight Canada's growing influence in the field of precision medicine.

## **Beyond the Genome: Transcriptome Based Diagnostics for Rare Diseases and Cancer**

**Project leaders:** Adam Shlien, James Dowling, Hospital for Sick Children

**Genome Centre:** Ontario Genomics

**Total funding:** \$3 million

Rare genetic diseases affect more than 500,000 children in Canada, often causing severe disability and early death, while cancer is the leading cause of non-accidental death in childhood. Early diagnosis at the molecular level is essential so that the right treatment for each individual can begin as early as possible. The most advanced genetic tests, however, are able to diagnose fewer than half of all children with rare disease and cannot detect important genetic changes in tumours that are critical for successful treatment.

In the first phase of this competition, Drs. Adam Shlien and James Dowling of the Hospital for Sick Children, with co-leaders Drs. Michael Wilson and Michael Brudno, demonstrated that RNA sequencing (RNA-seq), an emerging technology that examines the activity and structure of genes, can find disease-causing genetic variants (Dowling) and detect mutations and fusions in cancer genes (Shlien). Importantly, many of these mutations are not found by current genetic testing. In this second phase, they are combining their strengths to further develop and optimize the technological elements of RNA-seq and definitively determine how well it performs as a clinical test. Their goal is to create a clinically viable, comprehensive RNA-seq–based diagnostic platform for rare diseases and cancer. This platform will be fully automated, using advanced robotics and algorithms, and will improve in accuracy for every sample it is run on.

Their work will result in the first clinical RNA-seq diagnostic test in Canada. When fully implemented, the test will significantly increase the success rate of genetic testing in children with rare genetic diseases and cancer and improve access to clinical trials. The researchers will also create a dynamic digital library to integrate RNA-seq data with a range of health information, setting the stage for true precision medicine for all Canadians.

## **Interactome mapping of disease-related proteins using split intein-mediated protein ligation (SIMPL)**

**Project leader:** Igor Stagljar, University of Toronto

**Genome Centre:** Ontario Genomics

**Total funding:** \$2.2 million

Every cell in the human body contains proteins, and these proteins are essential to the proper functioning of every part of our body. Proteins are not soloists, though – like an ensemble, they interact with other proteins, in a process called protein-protein interactions, or PPIs. When these interactions go awry, disease results. Because of their involvement in causing diseases, understanding how these interactions work is essential to finding targets for intervention and developing drugs that will do so.

In phase 1 of this competition, Dr. Igor Stagljar of the University of Toronto and his team developed a new method for studying PPI interactions, called Split Intein-Mediated Protein Ligation (SIMPL), which outperforms current methods for studying PPIs. They now propose to further develop SIMPL as a groundbreaking assay for biomedical research by combining it with mass spectrometry to extend its capabilities and facilitate a more powerful and convenient platform. The team will also use SIMPL to globally map PPIs involved in disease, particularly cancer development. Finally, they will use SIMPL as a drug-screening platform to identify chemicals that can interfere in PPIs implicated in cancer development.

SIMPL will be a transformative technology for studying functional genomics. It will displace current methods of studying PPIs, accelerate our understanding of cell physiology and disease development and identify new therapies for some diseases. SIMPL will be commercialized through a newly founded Canadian company, ProteinNetwork Tx, ensuring both economic and health benefits for Canada.

**Development of a digital microfluidic platform to identify and target single cells from a heterogeneous cell population for lysis in an ultra-low volume for non-invasive prenatal diagnosis**

**Project leaders:** Aaron Wheeler, University of Toronto; Elena Kolomietz and David Chitayat, Sinai Health Systems

**Genome Centre:** Ontario Genomics

**Total funding:** \$3 million

Currently prenatal diagnosis, by amniocentesis or chorionic villi sampling, is costly, is being done only by specialists in a small number of centers and carries a risk of miscarriage. Amniocentesis is done later in pregnancy, with results often not known until 17 weeks gestation. To reduce the cost, these prenatal diagnostic tests are usually offered only after an earlier prenatal screening test result or fetal ultrasound shows an increased risk for chromosomal abnormality. A safe, non-invasive and less expensive procedure, which can be done by a variety of health care professionals, would allow testing of all pregnant women for fetal chromosome abnormalities, rather than only those at an increased risk, as well as testing for single gene disorders of pregnancies at risk. This will relieve parental anxiety while reducing healthcare costs, substantially.

Experts at Mount Sinai Hospital have developed a method to collect fetal cells non-invasively, using a technique similar to a PAP smear. In the first phase of this project, Dr. David Chitayat and Dr. Elena Kolomietz from Mount Sinai worked with Dr. Aaron Wheeler and his team at the University of Toronto to develop a way to isolate and analyze these cells using microfluidics and genomic analysis. The team built a proof-of-principle digital microfluidic platform that it will now further develop for beta testing and validation for accuracy, precision, sensitivity and specificity in a clinical laboratory, culminating in a 550-patient clinical trial.

This new technique could transform prenatal diagnosis, providing a safe, non-invasive and inexpensive diagnostic test that can be performed as early as six weeks of pregnancy. With no

other test like it available, it will compete in the multi-million dollar global market and save the healthcare system hundreds of millions of dollars. The technique will be commercialized through a start-up company that will attract investment and create job opportunities in Canada's burgeoning high-tech/biotech sector.

### **Digital Omics of Single Exosomes**

**Project leader:** David Juncker, McGill University

**Genome Centre:** Génome Québec

**Total funding:** \$2 million

Exosomes are tiny droplets secreted by cells and are made up of a thin lipid membrane (think of soap bubble), but only about 100 nanometer in size, filled with liquid, and packed with protein and nucleic acids. Exosomes have been recognized to play a critical role in many diseases, notably cancer. Indeed, exosomes are tiny "parcels" sent among cells, carrying information about the cell-of-origin – a fingerprint of the cell and the disease –that could reprogram the recipient cell, turn it into a cancerous cell, and thus promote cancer dissemination. Exosomes are found in abundance in blood, hence it should be possible to intercept these individual "parcels", decode their content, the cell-of-origin, and intended recipient cell. This information could be used to diagnose the disease much earlier, anticipate on its progression, which could in turn guide therapy and prevent progression. However, state-of-the art technologies for analyzing exosomes are not sufficiently sensitive, and hence thousands, if not millions of exosomes need to be aggregated and mashed up before they can be measured, whereby all information about individual exosomes is lost, and the signal from diseased cells cannot be distinguished from the healthy cells.

Dr. David Juncker of McGill University has been developing a new groundbreaking technology called Digital Omics of Single Exosomes (DOSE) for the analysis of millions of individual exosomes at a time. Thanks to funding in the first phase of Genome Canada's Disruptive Innovation in Genomics competition, the feasibility of DOSE was validated, and will now be developed as a platform technology for high-throughput single exosome analysis. Together with his partners, they will apply DOSE to study colorectal cancer liver metastasis (CRCLM), a common form of cancer affecting more than 13,000 Canadians per year with a death rate greater than 70 per cent. The team aims to identify exosomal fingerprints of CRCLM that may be used to gain understanding about this cancer, to develop blood-based diagnostic tests, and guide therapeutic interventions.

It is anticipated that the development of DOSE will pave the way for commercialization through a spin-off company that will provide instruments, reagents, services. DOSE could transform cancer research, clinical trials and overall cancer management, all with a simple, low-cost and non-invasive blood test. The development of the platform will create jobs for Canadians, attract investment and better position Canada in the \$40 billion cancer diagnostics market.

## **The RNA Zipcode Discovery Pipeline: Emerging tools for therapeutic targeting at subcellular resolution**

**Project leaders:** Eric Lécuyer, Institut de recherche clinique de Montréal (IRCM); Mathieu Blanchette, Jérôme Waldispühl, McGill University

**Genome Centre:** Génome Québec

**Total funding:** \$3.2 million

The human body is made up of trillions of cells, each of which has its own role to play in making our bodies function properly. To carry out their specified role, cells need to organize their inner components very precisely. If this organization is defective, we become susceptible to different diseases such as neuromuscular disorders or cancer.

The cell directs its components to the right place using an intricate addressing system, similar to the way postal codes get our mail to the right location. Dr. Eric Lécuyer and his team are working to increase our understanding of how this system works, focusing on RNA. In the first phase of this competition, the team developed methods to identify the “zipcodes” that are present in different kinds of RNA molecules, which help transport the RNA to specific places in the cell. Now the team plans to use these zipcodes as tools to target drugs to specific destinations inside our cells. The project will result in a proprietary prototype zipcode discovery platform, a collection of patentable RNA zipcodes that enhance the targeting of nucleic acid-based drugs, of RNA-based vaccines and of RNA editing systems, such as CRISPR.

By improving the delivery of therapeutic molecules at subcellular resolution, this project will speed up the development of drugs for currently incurable diseases, such as Myotonic Dystrophy type 1. The commercial value of the technologies will be captured through the creation, together with partner AmorChem, of a Montreal-based spin-off company.