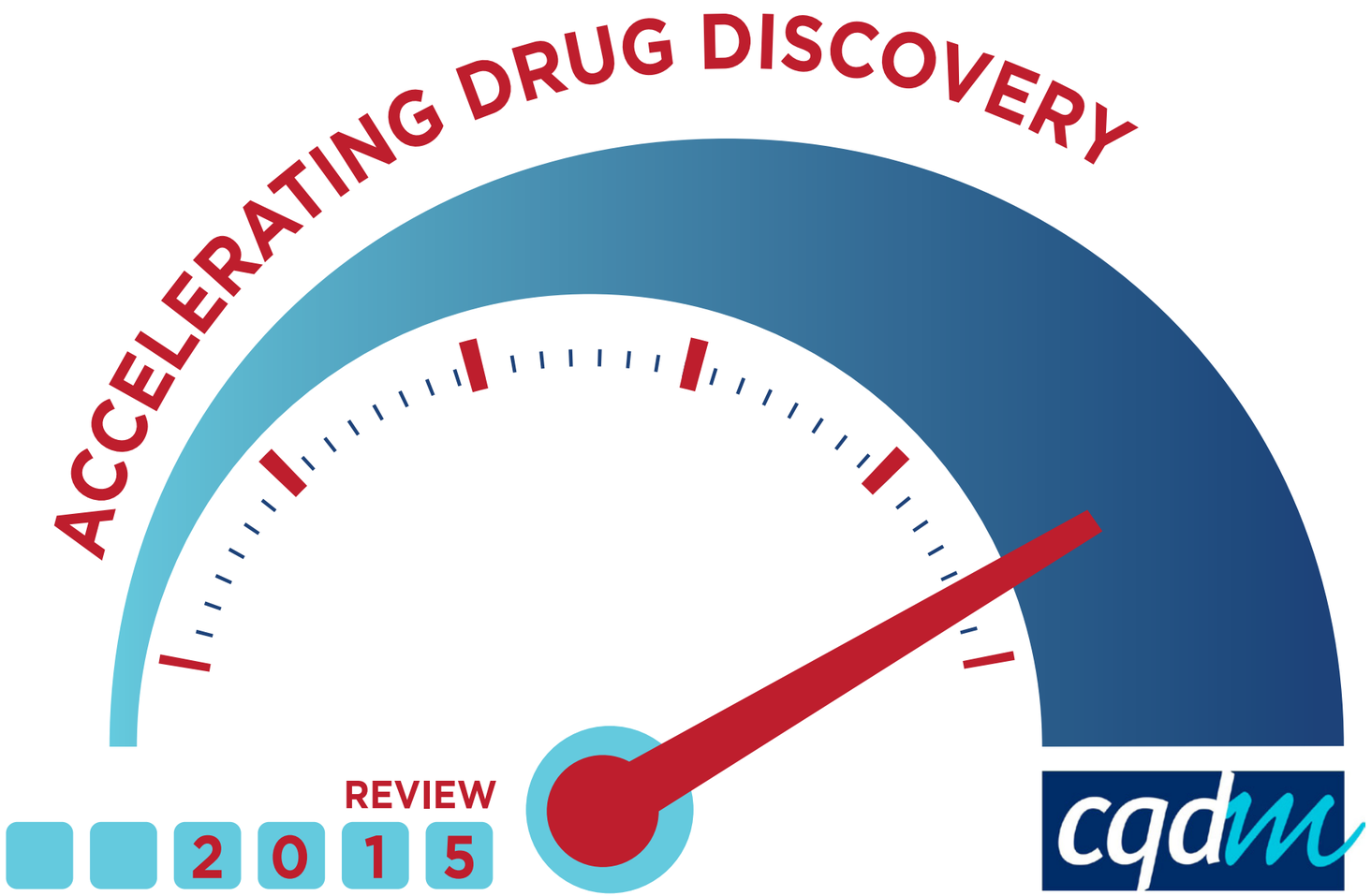
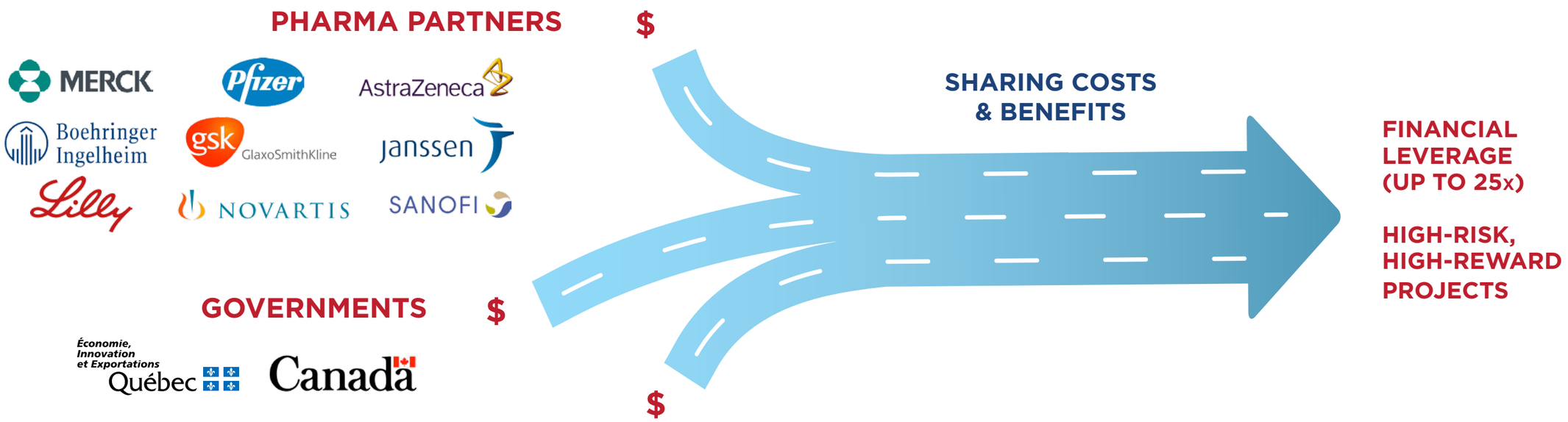

ACCELERATING DRUG DISCOVERY
REVIEW
2015
cqdm



We are a not-for-profit organization whose mission is to fund the development of breakthrough technologies that accelerate the discovery and development of new medicines.

We have the capacity to fund SMEs and academic institutions across Canada. The best projects are selected through a rigorous evaluation process organized within several calls for proposals.

We are also a driving belt that fosters strong collaborations amongst disciplines and institutions. We nurture partnerships between the pharma industry, SMEs and academia with the goal to generate significant economic benefits.

A UNIQUE BUSINESS MODEL

We have created an open innovation concept that brings nine (9) leading pharmaceutical companies to collaborate and share the costs of research together with two levels of government. Moreover, we are involving strategic co-funding partners who also contribute to fund research. These partners are located in Canada, the United States and Europe.

Our collaborative approach allows to generate an impressive financial leverage of up to 25x, bridging the gap in the innovation chain, de-risking early stage research, allowing funding for research projects which could not have been funded otherwise and helping bring innovative products and services to global markets.

ONE-OF-A-KIND MENTORSHIP PROGRAM

We have established a unique mentorship program which connects funded researchers with senior scientists from our pharmaceutical partners. The mentors offer valuable expertise and resources to help in the development of the projects and ensure that CQDM's funded research is aligned with the needs of the industry.

As of today, a total of 100 mentors from around the world have been involved in CQDM's projects. These win-win collaborations have been invaluable to the researchers and the mentors, and have led to many long-term partnerships.

WHO WE ARE

WE ASPIRE TO CREATE STRONG CANADIAN AND INTERNATIONAL NETWORKS DEDICATED TO ADVANCING NEXT-GENERATION TECHNOLOGIES IN ORDER TO BRING BETTER CURES TO PATIENTS.

2015 FUNDING PROGRAMS

CQDM manages several annual calls for proposals open to SMEs and academic researchers across Canada. Our funding programs nurture public-private and multi-institutional collaborations. Many of these programs are carried out in collaboration with strategic co-funding partners.

NATIONAL PROGRAMS

Ontario Centres of Excellence
Where Next Happens

CQDM EXPLORE PROGRAM IN PARTNERSHIP WITH ONTARIO CENTRES OF EXCELLENCE (OCE) (for SMEs and academic labs in Quebec and Ontario)
Supports early concept validation of unconventional, game-changing and highly innovative technological approaches.

Brain Canada Foundation

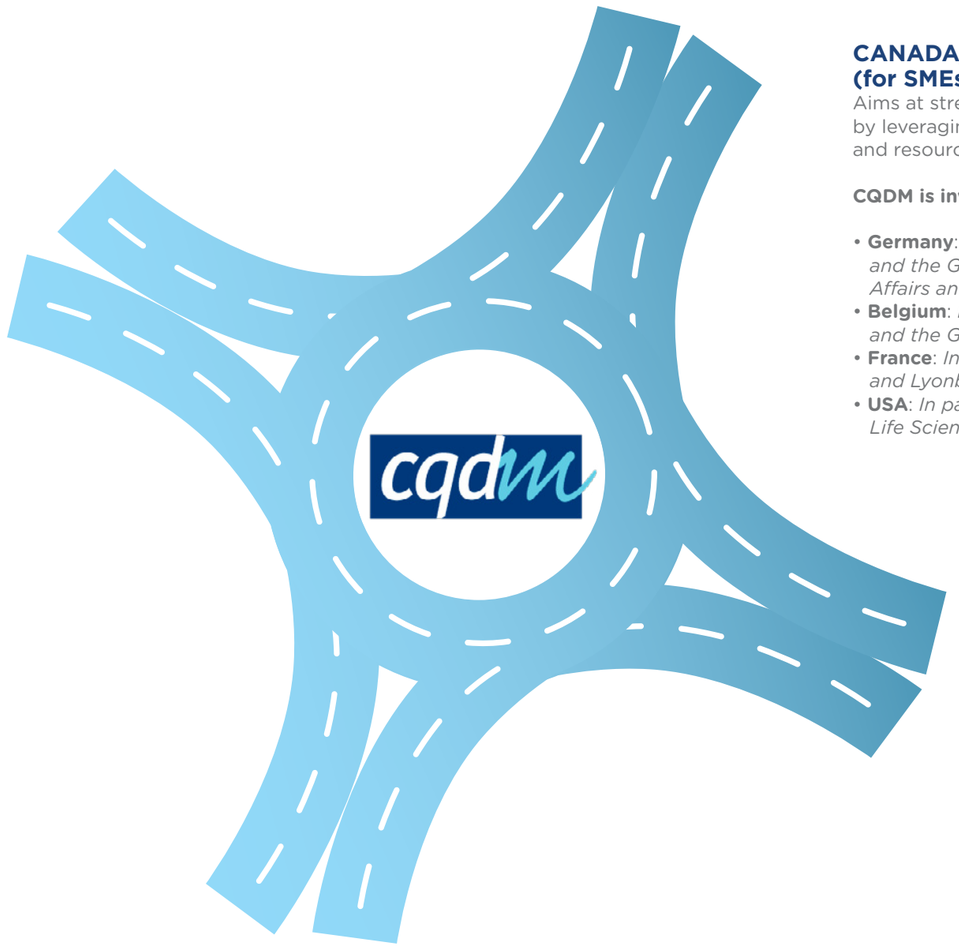
ONTARIO BRAIN INSTITUTE | INSTITUT ONTARIEN DU CERVEAU

FOCUS ON BRAIN PROGRAM IN PARTNERSHIP WITH BRAIN CANADA AND THE ONTARIO BRAIN INSTITUTE (OBI) (for SMEs and academic labs in Canada)
Aims at developing cutting-edge technologies, platforms or tools with immediate impact in neuroscience.

CIHR IRSC
Canadian Institutes of Health Research | Instituts de recherche en santé du Canada

CQDM/CIHR COLLABORATIVE PROGRAM IN PERSONALIZED MEDICINE (for SMEs and academic labs in Canada)
Funds novel technologies and tools to address critical challenges in personalized medicine.

QUANTUM LEAP PROGRAM (for SMEs and academic labs in Canada)
Aims at further developing cutting-edge platforms with exceptional impact on biopharmaceutical R&D, while positioning them advantageously for commercialization.



INTERNATIONAL PROGRAM

CANADA/EUROPE JOINT FUNDING INITIATIVE (for SMEs and academic labs in Canada)
Aims at strengthening biomedical research in Canada by leveraging complementary international expertise and resources.

CQDM is involved with partners in four countries:

- **Germany**: *In partnership with AiF Projekt and the German Federal Ministry for Economic Affairs and Energy;*
- **Belgium**: *In partnership with BioWin and the Government of Wallonia;*
- **France**: *In partnership with Alsace BioValley and Lyonbiopole;*
- **USA**: *In partnership with Massachusetts Life Science Center (MLSC).*

AiF Projekt GmbH

ZIM Zentrales Innovationsprogramm Mittelstand

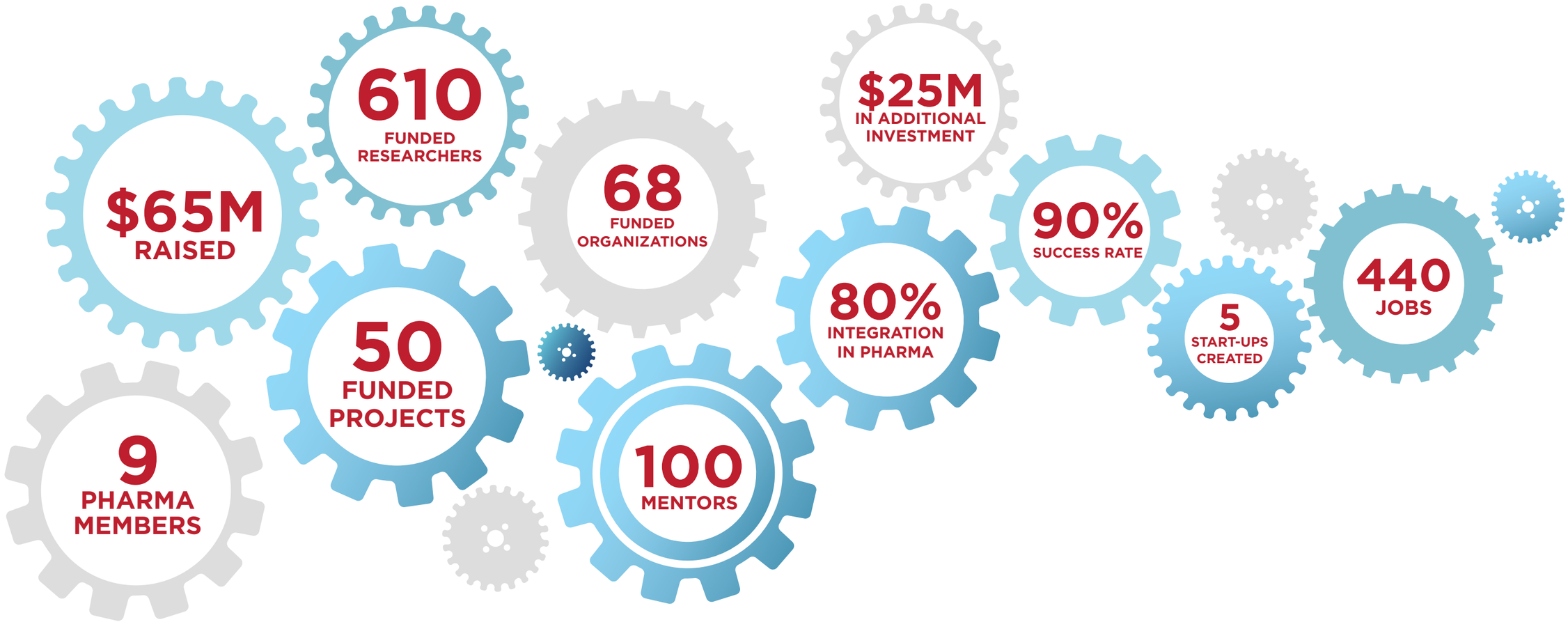
BioWin THE HEALTH CLUSTER OF WALLONIA

Wallonia.be

Alsace BioValley

LYONBIOPOLE

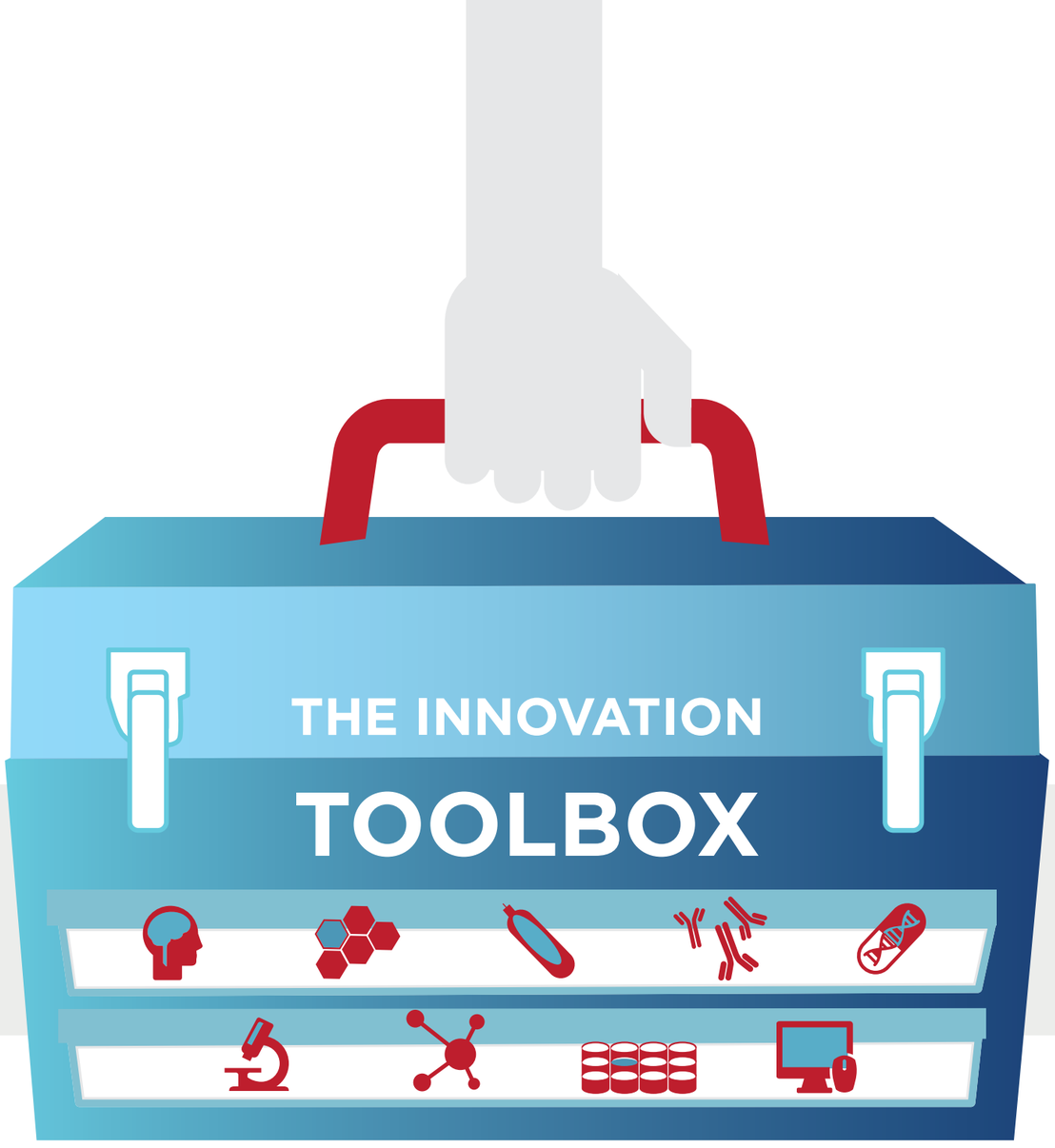
MASSACHUSETTS LIFE SCIENCES CENTER



CQDM BY THE NUMBERS

CQDM IS A UNIQUE PHARMA RESEARCH CONSORTIUM IN CANADA BASED ON:

- A collaborative approach that brings very strong financial leverage (up to 25 fold);
- The capacity to fund SMEs as well as academic labs;
- A mentorship program that forges strong links with the pharma industry, fostering long-term partnerships for SMEs and academia;
- A simple operational model to manage intellectual property for the benefit of all parties;
- A proven track record of results that strongly impact biopharmaceutical research.



CQDM'S PORTFOLIO OF PROJECTS

50 OUTSTANDING PROJECTS

OF THESE, 16 HAVE BEEN COMPLETED WITH A SUCCESS RATE OF 90%

CQDM filled a toolbox of innovative technologies that will impact the discovery or development of new medicines in four (4) meaningful ways:

- **Reducing the costs;**
- **Reducing the time to market;**
- **Reducing the risks or;**
- **Opening new research avenues.**

DISCOVER THE CQDM TOOLBOX !

NEURODEGENERATION & MENTAL HEALTH

1. DEVELOPING NEW ALZHEIMER'S THERAPEUTICS USING NOVEL BLOOD-BRAIN BARRIER CARRIER TECHNOLOGY

Investigators: **Nathan Yoganathan** and John Gillard (KalGene Pharmaceuticals Inc.), Louis Collins and Jean-Paul Soucy (Montreal Neurological Institute, McGill University), Danica Stanimirovic and Balu Chakravarthy (National Research Council Canada), Pedro Rosa-Neto (Douglas Hospital Research Centre) and Michael Waterston (Centre for Imaging Technology Commercialization - CIMTEC)
Date of initiation: May 2015 ***• $2.6M over 3 years in collaboration with Brain Canada, OBI and Kalgene***

Toxic amyloid proteins, proteins inappropriately folded in the body, are known to be a significant contributing factor in the development of Alzheimer's disease. Abnormal clusters of these protein fragments build up between nerve cells in the brain leading to impaired memory. Although biologics, antibodies and peptides that bind and neutralize toxic amyloid are in development, delivering sufficient quantities of such safe and effective compounds across the blood-brain barrier (BBB) in humans has not yet been possible. Combining their expertise, the research team has fused a peptide which can bind and inactivate toxic amyloid-beta proteins to an improved FC5 antibody fragment and showed in animal models that such fused compound can cross the BBB.

The goal of this project is to translate these results to humans. Upon generation of a fused compound and approval by Health Canada to perform this first study in humans, the team will demonstrate that such compound when injected in the blood of human subjects can be delivered to the brain, as detected in their cerebral spinal fluid. The fused compound will then be injected to ten patients with early, but detectable signs of Alzheimer's disease and to ten healthy volunteers. In addition to the analysis of the cerebral spinal fluid, positron emission tomography (PET) imaging will then be used to visualize the binding of the peptide to the amyloid-beta proteins. The results of this project will demonstrate the feasibility of effectively delivering therapeutic agents across the blood-brain barrier in humans. Moreover, imaging blood-brain carriers functioning in human subjects will not only accelerate the development of therapies for Alzheimer's, but also for other brain conditions.

2. USING HUMAN SINGLE-DOMAIN ANTIBODIES AND OTHER NOVEL APPROACHES TO CROSS THE BLOOD-BRAIN BARRIER

Investigators: **Rob Hutchison** and Reinhard Gabathuler (biOasis Technologies Inc.), Danica Stanimirovic (National Research Council of Canada), Brigitte Guérin, Roger Lecomte and David Fortin (Université de Sherbrooke)
Date of initiation: May 2015 ***• $2.6M over 3 years in collaboration with Brain Canada and NRC***

The blood-brain barrier (BBB) is a tightly woven layer of vascular cells that prevents harmful molecules from the circulation, viruses and toxins to enter the brain. Unfortunately, this barrier is also an obstacle for the delivery of therapeutics to treat brain diseases.

To overcome this problem, the researchers will develop miniaturized human single-domain antibodies as molecular Trojan horses and other novel approaches to enable delivery of therapeutics across the blood-brain barrier. Partners in this project have unmatched complementary expertise in developing, evaluating (NRC and Sherbrooke) and commercializing (biOasis) brain delivery technologies.

To identify the Trojan horses, the team will screen thousands of antibodies from their library and choose those that can efficiently cross the BBB and be simultaneously linked to many different therapeutic molecules. The researchers will then develop 'fusion' molecules consisting of the BBB-crossing mini-antibodies and selected therapeutics in order to achieve brain selectivity, improve transport capacity and design modularity. The efficacy of these 'fusion' molecules in treating brain diseases such as brain tumours will be tested in preclinical models. During these studies, new non-invasive imaging methods by positron emission tomography (PET) scan will be developed to monitor brain penetration of BBB-crossing antibodies.

By funding this partnership between academia and biotech researchers, CQDM and Brain Canada provide means to selectively open the door of the blood-brain barrier to many new therapeutic agents which currently remain blocked at the gate. More importantly, it will allow biOasis to bring such therapeutics to the patients.

3. NON-INVASIVE IDENTIFICATION OF AB PLAQUES IN HUMAN RETINA FOR THE DIAGNOSIS OF ALZHEIMER'S DISEASE

Investigators: **Jean-Paul Soucy** (McGill University), Frédéric Lesage (Polytechnique Montréal), Sandra Black (Sunnybrook Research Institute), Jean-Philippe Sylvestre (Optina Diagnostics), Jean Daniel Arbour (Université de Montreal), Pedro Rosa-Neto (Douglas Hospital Research Centre), Barry Greenberg (Toronto Western Research Institute), Chris Hudson (University of Waterloo), and Daniel L. Farkas (The Brain Window, Inc.)
Date of initiation: May 2015 ***• $1.5M over 3 years in collaboration with Brain Canada and OBI***

The ability to diagnose Alzheimer's disease (AD) at an early stage would lead to a better understanding of its genesis in addition to radically transforming the design of clinical trials in order to develop new treatments. The eye offers a natural window to the brain as the retina is an extension of the brain. The presence of beta amyloid (Aß) plaques in the retina of Alzheimer's disease preclinical models and humans was recently reported, opening the possibility of detecting this AD hallmark through a simple non-invasive eye scan.

With this project, the team will develop a retinal imaging platform using spectrally resolved fluorescence combined with advanced imaging instruments to detect Aß plaques in the retina of patients, and validate the method against brain Aß plaques seen on amyloid PET imaging. The team will assess a clinical cohort of 350 volunteers aged 60 years or more at different stages of development problems of brain function (controls, mild cognitive impairment and dementia level AD subjects). This novel imaging platform will enable the detection and early diagnosis of the disease in at-risk patients which will facilitate the development of drugs to treat Alzheimer's disease.

4. MRI-BASED METHOD TO MEASURE METABOLIC AND VASCULAR ANOMALIES IN THE BRAIN OF PATIENTS WITH ALZHEIMER'S DISEASE

Investigators: **Richard Hoge**, Pierre Bellec, Sylvie Belleville, Oury Monchi, Yan Deschaintre, Julien Doyon (Institut universitaire de gériatrie - Université de Montréal), Christian Bocti (Université de Sherbrooke), Serge Gauthier (McGill University), and Douglas Arnold (NeuroRx)
Date of initiation: September 2012 ***• $1.5M over 3 years***

Being able to detect Alzheimer's disease (AD) at an early stage could help slow down its progression. The project led by Richard Hoge aims at developing an innovative methodology that allows for rapid and non-invasive imaging of mitochondrial dysfunction as a biomarker for early-stage diagnosis of AD. Detailed exploration of mitochondrial impairment is obtained by measuring the oxidative metabolism and vascular anomalies in the human brain. This approach, termed QUO2 (QUantitative O2) magnetic resonance imaging enables radiation-free, non-invasive imaging with high spatial resolution and sensitivity.

Eighty (80) AD patients and eighty (80) matched controls will be enrolled to undergo QUO2 as well as complementary MRI, PET, blood work and neuropsychology testing. Preliminary results already pinpoint differences between AD patients and controls, particularly the widespread reductions of cerebrovascular reactivity in AD patients. The resulting non-invasive technology could thus likely be used as a biomarker to diagnose and stratify AD patients at an earlier stage and to follow disease progression in clinical trials.

5. DIAGNOSTIC TEST USING LIGHT TO NON-INVASIVELY PROFILE PATIENTS WITH SCHIZOPHRENIA AND BIPOLAR DISORDER

***completed project**
Investigators: **Michel Maziade**, Marc Hébert, Chantal Mérette, Roch-Hugo Bouchard, Marie-Josée Filteau and Marc-André Roy (Centre de recherche de l'Institut universitaire en santé mentale de Québec -Université Laval) ***• $2.1M over 3 years***

In this project, the team has developed non-invasive biomarkers to diagnose more accurately and at an early stage, patients with schizophrenia or bipolar disorder, allowing for better treatments while reducing health and social costs. This exceptional approach allows to stratify such patients using electroretinography (ERG) profiles, which relies on the use of the retinal response to light stimulation to access and monitor the central nervous system.

From a cohort of 150 schizophrenia and 150 bipolar disorder patients as well as 200 healthy volunteers (controls), highly predictive ERG-based biomarkers for the differential diagnosis of major psychoses (sensitivity up to 95% and specificity up to 80% to distinguish between schizophrenia and bipolar patients) were developed. Moreover, when ERG analysis was applied to psychotic patients taking antipsychotic molecules, the team observed that these medications displayed a specific ERG signature identifying better and poorer responders with 100% sensitivity and specificity for olanzapine and up to 97% for quetiapine and lithium.

These results demonstrate that ERG profiles can predict a patient's susceptibility to respond to a specific therapeutic molecule. It could thus help to reduce patient recruitment time, leading to impressive clinical trial cost savings while also reducing mental health costs due to earlier diagnosis of schizophrenia and bipolar disorder patients.

Following these successes, the team was awarded a grant of $750K from CIHR to develop a predictive test for children at high risk of developing schizophrenia and bipolar disorder. Moreover, the start-up DiaMentis was recently created to commercialize this first biological tool in psychiatry for diagnosing major psychoses.

6. MULTIMODAL IMAGING PLATFORM FOR EARLY DIAGNOSIS OF PARKINSON'S DISEASE AND PREDICTIVE MODELS

Investigators: **Barry Bedell** (Biospective Inc.)
and **Jack Hopin** (inviCRO)
Date of initiation: October 2014 *• $1M over 18 months in collaboration with MLSC, Biospective and inviCRO*

Parkinson's disease (PD) is characterized by motor symptoms, as well as disorders of cognition, speech, mood, and behaviour. While PD is currently diagnosed based on motor impairment, the non-motor deficits (the prodromal stage) typically precede the cardinal motor symptoms by several years. PD is associated with the presence of Lewy bodies and neurites composed of misfolded fibrillar α-synuclein. The recent development of animal models of α-synucleinopathy allows preclinical assessment of putative "anti-synuclein" therapies. However, non-invasive imaging of these models is lacking.

By combining their complementary expertise in the field of medical imaging, Biospective and inviCRO will characterize early pathological changes in α-synuclein mouse models, using state-of-the-art, multi-modality imaging techniques. The team will develop novel MRI and SPECT (single photon computerized tomography) biomarkers. This "imaging phenotype" for PD mouse models will expand the range of unique services offered by the two companies, while also accelerating preclinical drug development treatments or prevention of this disease and facilitating the transition to patient selection and monitoring in clinical studies.

7. PHENOTYPING OF NEW MOUSE MODELS OF ALZHEIMER'S DISEASE

Investigator: **Barry Bedell** (Biospective Inc.)
Date of initiation: August 2012 *• $1.8M over 3 years in collaboration with Merck, Pfizer and Biospective*

In order to maximize the information obtained from MRI and PET imaging studies of animal models for Alzheimer's disease, it is vital to link such macroscopic imaging measures with the underlying microscopic pathological processes. With its innovative suite of image processing analysis tools, Biospective is well positioned to do so. In this project, new animal models for Alzheimer's disease are being developed by Merck and Pfizer (two knock-in mice in which the murine genes are replaced by the human tau or the human mutant amyloid precursor protein [APP]). Using its unique image analysis platforms, NIGHTWING™ and PERMITS™, Biospective has undertaken an in-depth characterization of these animal models. Novel neuroimaging and quantitative neuropathology endpoints will be included to study disease progression with the ability to evaluate responses to treatment. This project will advance basic research and drug discovery in the Alzheimer's disease field.

8. A REVOLUTIONARY PROBE FOR *IN VIVO* STUDIES OF THE BRAIN

Investigators: **Janusz Pawliszyn** (University of Waterloo), Dajana Vuckovic (Concordia University) and Clement Hamani (Centre for Addiction and Mental Health)
Date of initiation: May 2015 *• $995k over 3 years in collaboration with Brain Canada and OBI*

This project responds to the need to create an effective integrated analytical platform that improves the quality of *in vivo* analysis during the drug discovery process for the central nervous system and minimizes the use of laboratory animals. The platform is based on a low-invasive, non-lethal solid phase microextraction technology, which combines multiple steps of sample preparation, metabolism profiling and extraction for direct *in vivo* sampling in the brain. The approach involves the use of thinly coated biocompatible microwires to perform a chemical biopsy of the brain of a living subject without the need for tissue removal.

Due to their small dimensions and localized actions, these probes provide excellent spatial resolution and enable longitudinal studies on the same subject. The extraction of a wide range of targeted or non-targeted compounds is then coupled with mass spectrometry analysis to provide a sensitive preclinical profiling analysis of the drug biodistribution in the brain, the metabolic pathways affected by the drug as well as in depth cerebral chemical imaging.

The revolutionary technology of Professor Pawliszyn's team will thus provide a new and complementary platform to microdialysis while capturing not only elements of the lipidome and metabolome, but also *in vivo* observation of the long-term effects of drugs on the brain of a single living being. Moreover, by eliminating the statistical variability between subjects, this new technology will reduce the cost associated with personalized response in drug therapy studies and accelerate the drug development process.

9. AUTOMATED ZEBRAFISH HIGH-THROUGHPUT SCREENING TECHNOLOGY PLATFORM TO ACCELERATE SCREENING OF ANTI-AGGREGATION COMPOUNDS FOR PROTEIN MISFOLDING DISEASES

Investigators: **Xiao-Yan Wen** (St. Michael's Hospital), **Pierre Drapeau** (Université de Montréal) and Christopher Barden (Treventis Corporation)
Date of initiation: August 2014 *• $900k over 3 years in collaboration with OCE, Treventis Corporation and St. Michael's Hospital*

Protein misfolding and aggregation are implicated in diverse neurodegenerative diseases, such as Alzheimer's, frontotemporal dementia, Parkinson's, amyotrophic lateral sclerosis (ALS) and other chronic diseases such as diabetes.

The research team will develop an integrated, automated and validated high-throughput zebrafish screening platform (behavior, bioluminescence and fluorescence), as well as new zebrafish lines using existing and new zebrafish disease models for Alzheimer's disease (TAU), ALS (motor neurone) and diabetes (gluconeogenesis). This technology will be validated by screening Treventis' library of anti-aggregating compounds to identify small molecules (hits) against Alzheimer's disease and ALS.

By identifying hits at least 10 times faster than current manual *in vivo* screening protocols, this promising fully integrated technology brings to the industry important cost and time savings in the drug discovery process.

10. CYTO-IGLUSNFR: A GLUTAMATE BIOSENSOR PLATFORM FOR BRAIN DISEASES

Investigators: **Don van Meyel** and Keith K. Murai (Research Institute, McGill University Health Centre), Adriana Di Polo (Centre de recherche du Centre Hospitalier de l'Université de Montréal), and Timothy H. Murphy (University of British Columbia)
Date of initiation: May 2015 *• $1.4M over 3 years in collaboration with Brain Canada*

In the human brain and retina, glutamate (controlled by Excitatory Amino Acid Transporters or EAATs proteins in glial cells) is a very important messenger that carries information from one neuron to another. The level of glutamate transmitted between neurons is tightly controlled and can contribute to neurological diseases including stroke and Alzheimer's disease. EAATs are thus very attractive drug targets, however there are no comprehensive *in vivo* platforms to directly and dynamically interrogate EAAT-dependent glutamate transport within cells.

Cyto-iGluSnFR is a revolutionary protein engineering technology that the team intends to adapt for the discovery of EAAT-targeting drugs to treat a variety of brain and eye diseases. Cyto-iGluSnFR is based on a modified protein that senses glutamate, allowing one to measure the rate by which glutamate enters cells. The team plans to improve this glutamate biosensor and derive new cell lines to enable millions of chemicals to be screened in order to find drugs that make EAATs either more or less effective at moving glutamate into glial cells. The research team will also generate conditional knock-in mice carrying different alleles of Cyto-iGluSnFR with low, medium or high affinity for glutamate. These new animal models, where neurons and glial cells function as they do in humans, will be used to test potential drugs to ensure that they are safe and effective for patients.

11. OPTICAL IMAGING AND BIOSIMULATION PLATFORM TO ACCELERATE CNS DRUG DISCOVERY

Investigators: **Sébastien Blais-Ouellette** (Photon etc.), **Serge Bischoff** (Rhenovia Pharma), and Paul De Koninck (Université Laval)
Date of initiation: July 2012 *• $1.32M over 3 years in collaboration with Alsace BioValley*

Fundamental mechanisms underlying diseases of the central nervous systems (CNS), such as Alzheimer's, Parkinson's, schizophrenia, depression and autism, remain ill-defined in part due to a lack of proper methods for investigating complex molecular processes, such as spatial protein dynamics at the synapse level.

With this project, the team aimed at filling this gap by developing a highly innovative platform to gain a better understanding of receptor dynamics. They have designed quantum dot probes to label multiple receptors in neurons which could be simultaneously detected with the novel multiplexed optical cellular and subcellular imaging system they have developed. As a proof of concept, the team demonstrated the simultaneous detection and movement of Stargazin, GluA2, mGlur5 and GluA1 on a live neuron. Based on Photon etc.'s highly sensitive hyper-spectral detection technology capable of broad wavelength (500–850 nm) coverage for cellular imaging, this fluorescence imaging platform is fully functional, can currently detect up to 5 different labels, but has the potential to simultaneously detect dozens of labels as new adapted labels become available. The platform is now in operation at the Neurophotonics Centre.

12. VALIDATION OF CATECHOLAMINE-REGULATED PROTEIN 40 (CRP40) AS A MARKER FOR PARKINSON'S DISEASE

Investigators: **Ram Mishra** (McMaster University) and **Thérèse Di Paolo** (Université Laval), Joseph Gabriele (CRP40 Inc./McMaster University) and Pierre Blanchet (Université de Montréal)
Date of initiation: April 2012 *• $750k over 3 years*

Parkinson's disease (PD) for which there is currently no blood diagnostic assay, is a progressive neurodegenerative movement disorder afflicting 1 to 2% of the population over 65 years of age. This project aims at developing a biomarker which may provide a novel and unique blood test to diagnose PD more accurately.

The team hypothesized that catecholamine-regulated protein 40 (CRP40) could be used as a marker because of its dopaminergic and neuroprotective features. The researchers analyzed CRP40 mRNA (PCR) levels in the blood of more than 280 individuals including patients newly diagnosed with PD (drug naïve or taking dopaminergic drugs), patients with either Alzheimer's disease or stroke and healthy age-matched controls as well as in non-human primate models of PD. Unfortunately, human and non-human primate CRP40 blood mRNA levels were hard to assess, while in humans, it was not possible to distinguish unequivocally patients affected by the different neurodegenerative disorders.

However, the CRP40 protein level was also analysed in blood samples from few patients using a CRP40 ELISA developed by the research team. Interestingly and although preliminary, a decrease of serum CRP40 protein level seems associated with multiple neurodegenerative pathologies including Alzheimer's and Parkinson's diseases as well as stroke. The same ELISA is also working well in PD non-human primate models where it showed a decrease and could thus be used to monitor the response to new treatments. CRP40 Inc. is now working to improve the specificity of its ELISA assay.

ONCOLOGY

13. qTAP: A NOVEL PLATFORM FOR PERSONALIZED MEDICINE IN CANCER

Investigators: **Jeff Wrana**, Alexandre Zlotta, and Anne-Claude Gingras (Mount Sinai Hospital), Andrei Yudin (University of Toronto), Andrew Roughton (Encycle Therapeutics) and Azar Azad (Mount Sinai Services)
Date of initiation: July 2015 *• **$1M over 2.5 years in collaboration with CIHR, Encycle Therapeutics and Mount Sinai Services***

In the last decade, cancer genomics has shown that not all patient tumours are identical, and conversely that they will not respond similarly to particular anticancer agents. The key, therefore is personalized (or precision) medicine whereby specific drugs will be given to a patient carrying a gene that will make his/her tumours sensitive to such drug. This project proposes to develop qTAP (Quantitative Transcriptomics and Affinity Proteomics), a transformative diagnostic platform that will provide a global view (RNA and protein) of an individual patient's tumour. In particular, the research team will combine proteomics (mass spectrometry protein analysis) and transcriptomics to analyse breast and bladder tumours. By performing such molecular dissection of the tumours, qTAP will also identify new gene mutations and may reveal why different cancers respond differently to the same intervention, as well as the mechanisms underlying relapse and acquisition of therapeutic resistance. Such tumour "fingerprints" will likely identify targets for which new or current drugs might be effective.

To further establish their proof of concept, the researchers will treat human breast and bladder cancer cell lines with small molecules (including some developed during this project) directed against TGF beta and Hippo pathways and apply qTAP to visualize the molecular pathways affected by such treatments.

By developing qTAP, Wrana's team will enable clinicians to perform personalized medicine and design customised treatments involving optimal drug combinations that will provide patients with a more effective cancer therapy to prevent relapse commonly observed in clinics.

14. PERSONALIZED MEDICINE 2.0: INTEGRATED FUNCTIONAL AND GENOMIC PROFILING TO DETERMINE OPTIMUM COMBINATION THERAPY FOR CANCER PATIENTS

Investigators: **Mathieu Perrée** (DiaTech Oncology Inc., Montreal) and **Stephen Lyle** (Kew Group Inc., Boston)
Date of initiation: November 2015 *• **$1.975M over 2 years in collaboration with MLSC, Exactis, DiaTech and Kew Group***

While molecular profiling for the identification of potentially useful targeted therapies and the testing of functional tumour response to traditional chemotherapies are both useful approaches to personalizing a patient's treatment, rarely are both approaches to precision medicine utilized in an integrated manner.

This collaborative project stems from the complementarity of expertise of DiaTech Oncology in Montreal (Quebec), a diagnostic laboratory business with a unique assay testing functional chemotherapy response, and Kew Group in Boston (Massachusetts), a leading provider of molecular profiling of patient tumours to advance the broad implementation of personalized medicine into routine clinical practice.

The researchers hypothesized that combining functional (DiaTech Oncology technology) and genomic profiling (Kew Group technology) to analyse biopsy samples from individual patients will offer more robust and varied treatment options than either technology alone. By applying their assays on two distinct cohorts of 200 patients affected by either ovarian or breast cancer, the researchers will not only determine which genes are mutated in their tumours, but also identify their functional resistance and sensitivity to chemotherapies. The identification of such gene mutations could also pinpoint to new targets for therapies, while the functional assays will identify the most effective drugs among the traditional chemotherapies and eliminate treatments that could not induce apoptosis of the patient tumour cells. By eventually providing the results of such combined analysis to clinicians, patients could thus have access to better treatments and really benefit from personalized medicine.

15. *IN VITRO* SCREENING TOOL FOR PREDICTING EFFICACY OF DRUG CANDIDATES FOR OVARIAN CANCER

***completed project**
Investigators: **Anne-Marie Mes-Masson** (Université de Montréal), Frédéric Lesage and Thomas Gervais (Polytechnique Montréal) *• **$300k over 2 years***

Only a portion of women diagnosed with ovarian cancer will respond to current therapies. To better tailor treatment, the team proposed a novel approach whereby the tumour cells themselves are tested for their response to multiple drugs.

Similar systems developed before have failed because they did not take into account the specific features of the tumour tissue and environment, were not economical, and could not be performed rapidly enough to influence clinical decision-making.

To address these concerns, the research team has developed an innovative, multilayer microfluidic device within which ovarian 3D spheroids or cancer tissues can be maintained to assess tumour-based drug response *in vitro* and compared *in vivo* results for a given patient. Since both cells and tissues can be cultured (and treated with anticancer agents) for at least 10 days within these devices, they are thus suitable for clinical decision-making. Indeed, treating tumour samples with carboplatin demonstrated that the cells from this patient responded to the drug, which correlates with the clinical response seen in the patient. The team has therefore developed a microfluidic system that tests the sensitivity of tumour cells to chemotherapeutic agents in a time frame compatible with patient treatments. Moreover, such a platform could also be used to test new compounds against multiple solid tumour types including prostate, breast, colon, and lung cancer.

16. INTEGRATING TUMOUR MICROENVIRONMENT BIOMARKERS TO IMPROVE TARGETED BREAST CANCER THERAPY

Investigators: **Morag Park**, Michael Hallett and Atilla Omeroglu (McGill University)
Date of initiation: September 2011 *• **$1.3M over 3 years***

It has become increasingly clear that breast cancer progression, response to therapy and ultimately outcomes are determined not only by features of the tumour itself, but also by characteristics of and interactions with the surrounding tissue, or stroma. Presently, stromal information is not used for patient stratification in the clinical setting, trial design or retrospective analyses of drug efficacy due to the lack of standardized tests suitable for assigning tumour samples to specific stromal subclasses.

With this project, Morag Park and her team have used gene expression profiling and TaqMan technology to establish mRNA as well as microRNA signatures of tumours and matched stroma obtained from subtypes of poor-outcome breast cancers from 118 patients. The research team has already demonstrated that incorporating stromal gene and miRNA expressions allows for a better stratification of patients than tumour gene expression alone. They have now identified 4 new stroma-defined gene expression-based profiles, which when applied to large external datasets (n=1098) reveal association with outcomes within triple negative disease ($p<0.05$). A novel stratification scheme for triple-negative disease based on immune cell localization has been developed. These advances in our understanding of how stroma exerts a multifactorial effect on disease outcome will allow improved identification and stratification of patients who are unlikely to respond to current treatments, as well as the development of personalized therapeutic strategies targeting specific disease configurations defined by intersections of tumour-intrinsic and stromal properties.

17. NEW BIOMARKERS FOR NEUROENDOCRINE CANCER

***completed project**
Investigators: **Daniel Chelsky**, Eustache Paramithiotis, Joël Lanoix (Caprion Proteomics Inc.) and **Stéphane Gasman** (CNRS) *• **$740k and €300k over 3 years in collaboration with French partners and Caprion***

Neuroendocrine tumours are very difficult to diagnose correctly and are rarely detected at an early stage. Since existing treatments are not effective in late stage tumours, there is an urgent need to improve diagnosis and develop more effective and specific therapies against these tumours. To fulfill this need, the team used Caprion's large scale proteomics approach on both neuroendocrine cancer cell lines and tumour-derived tissues. Neuroendocrine tumours are characterized by the presence of secretory granules and can release polypeptide hormones and biogenic amines such as serotonin. Considering that the aggressiveness of these tumours appears related to their level of secretion, the researchers concentrated their efforts on secreted protein biomarkers. Of the many differentially expressed proteins identified, over 100 were selected on the basis of biological as well as quantitative criteria. These candidate diagnostic biomarkers were tested for their expression in sera from subjects with either benign or malignant pheochromocytomas or healthy controls using a targeted and quantitative "multiple reaction monitoring" mass spectrometry (MRM-MS) assay. Promising preliminary data suggest that some of these biomarkers have the potential to become the basis of an accurate blood test. In parallel, a set of nine (9) candidate therapeutic targets were selected and appear to have important roles in cell proliferation and tumour growth. Silencing many of these proteins *in vitro* resulted in significant inhibition of secretion, suggesting that they impact the secretory activity of cells and therefore represent novel and attractive therapeutic targets which may also facilitate diagnosis and patient stratification. Caprion is now actively pursuing the further characterization of these markers.

18. CHARACTERIZING BLOOD CIRCULATING TUMOUR CELLS (CTCs) TO USE THEM AS SCREENING TOOLS AGAINST ANTICANCER DRUGS

***completed project**
Investigators: **Richard Kremer** (McGill University) and Catalin Mihalcioiu (McGill University Health Center)
• $300k over 2 years

The major challenge in cancer therapy is to stop cancer cells before they metastasize to other tissues, at which point the disease becomes resistant to most forms of therapeutic interventions. During cancer progression, circulating tumour cells (CTCs) are shed from the primary tumour or its metastatic sites and their number follow closely the progression or regression of the disease. However, CTCs circulate in very low numbers making it difficult to isolate and study them using standard blood test procedures.

To overcome this limitation, the team of Richard Kremer and Catalin Mihalcioiu has used aphaeresis to isolate and expand CTCs from the blood of seven triple negative breast cancer patients. Using a new isolation strategy based on elimination of cell subsets bearing a panel of surface markers, the researchers have isolated and cultured CTCs in high enough numbers to be characterized, stored for later use, and used for drug sensitivity assays. A proof of concept was established by treating these cells with either Taxol™ or doxorubicin. Results of the next generation sequencing demonstrated the heterogeneity of the CTC populations and will allow to link the response to chemotherapeutic agents to the gene mutations they carry. Isolating CTCs using the aphaeresis protocol developed in this project could be applied to a variety of cancer types in the near future. In addition, characterization of such CTCs will open the doors to personalized medicine.

19. FACILITATING ANTICANCER DRUG DISCOVERY WITH SELECTIVE INHIBITORS OF UBIQUITIN

Investigators: **El Bachir Affar** (Centre de recherche de l'Hôpital Maisonneuve-Rosemont, Université de Montréal) and Sachdev Sidhu (University of Toronto)
Date of initiation: June 2015 ***• $300k over 2 years in collaboration with OCE***

Human cells dispose of non-functional proteins using a highly sophisticated degradation system called the ubiquitin proteasome system (UPS), in which enzymes attach a small protein called ubiquitin to damaged proteins. However, abnormalities in protein degradation are frequently observed in many diseases, including several types of cancer. As such, UPS enzymes could be novel targets for drug development but unfortunately, the paucity of selective molecules that modulate their function has severely hampered attempts to manipulate them for therapeutic benefits.

To overcome this limitation, the team will use a protein engineering technology to introduce mutations in ubiquitin to generate highly specific and potent ubiquitin-like molecules that associate tightly with these enzymes in a manner that will either block their catalytic function (inhibitors) or enhance it (activators). The binding of these molecules to their targets will first be validated using *in vitro*-based assays, while their inhibitory or enhancing functions will be assessed using relevant mammalian cell models. The researchers have already shown the proof of concept of this approach on some UPS enzymes, including E2 and the HECT class of E3 ligases. This project will allow them to target a different set of E3 ligases in which ubiquitinated proteins are implicated in cancer progression and response to therapy such as p53, thus enlarging the spectrum of cellular targets associated with cancer. Considering that p53 is involved in more than 50% of all cancers, this project represents a significant step towards the development of novel therapeutic molecules for many forms of cancer.

20. GENETIC INTERACTION STUDIES TO BETTER ESTABLISH EFFICACIOUS DRUG TARGETS

Investigators: **Tomas Babak** and Xiaolong Yang (Queen's University)
Date of initiation: June 2015 ***• $300k over 2 years in collaboration with OCE***

Genetic interaction networks, representing phenotypic changes resulting from perturbing the coding sequence of two or more genes, have emerged as one of the most powerful systematic approaches to understand the function of a cell. Mainly due to cost and technical limitations, such an approach has been applicable so far only in yeast.

To bring this technology one step further, the researchers are thus planning to generate interaction networks that will: i) work in human cells; ii) be sufficiently high-throughput to enable genome-wide interaction screens; and iii) simultaneously detect effects of single, pairwise and triple gene knockouts. To be optimal, this process should take a few days and cost less than $1,000 per screen. Such disruptive technology will have an impact at all stages of drug development, including the discovery of novel drug targets. The key to this technology is to tag each cell with a unique barcode that tracks that particular genetic interaction within a pool of cells. By merging two established approaches – CRISPR/Cas9 engineering and global genetic interaction network screening – the researchers will comprehensively map interactions between disease pathways and all known genes. By applying this technology to complementary environmental backgrounds, this approach could for example: i) identify new targets in presence (vs. absence) of drug candidates; ii) identify new biomarkers using models of disease progression; and iii) associate drug efficacy with personal genomics.

21. SYNTHETIC LETHALITY PLATFORM TO DISCOVER, TEST AND VALIDATE NEW THERAPEUTIC TREATMENT OPTIONS FOR CANCER

***completed project**
Investigators: **Gordon Shore**, William Muller, Jerry Pelletier, Nahum Sonenberg and Michel Tremblay (McGill University)
• $2M over 3 years

This platform allows to discover, test and validate new cancer therapeutic treatment options based on synthetic lethality. This concept refers to a requirement that two genes, if eliminated individually, have little impact on cancer cells, but result in cell lethality when impaired together. Combining two anticancer drugs that are moderately effective when used alone into a potent killer mixture is one way to do it. Another method is to utilize a drug in a patient population in which the second gene is mutated, promoting the drug's efficacy.

The project has delivered human siRNA/shRNA libraries and computational methods for high-throughput-based identification of candidate synthetic lethal genes. A proof-of-concept was conducted in multiple myeloma with a focus on genetic markers of sensitivity to dexamethasone. As a result, three potential clinical strategies involving drug combinations were identified and validated *in vitro*. A second synthetic lethal siRNA screen involving the novel antimitotic DZ2384 has revealed a number of candidate drug targets for this compound as well as potential drug combinations for future clinical development. The platform was instrumental in generating a promising discovery for Diazon Pharmaceuticals, a Montreal start-up funded by Sanderling, a top-tier American venture firm.

DIABETES

22. DRUG SCREENING PLATFORM USING A BIOARTIFICIAL PANCREAS MODEL

Investigators: **Patrick Vermette** (Université de Sherbrooke) and **Séverine Sigrist** (Centre européen d'étude du diabète) and Richard Bou Aoun (Defymed)
Date of initiation: May 2014 ***• $377k and €512k over 3 years in collaboration with French partners***

Islet transplantation has been shown to be an efficient therapy to reverse type 1 diabetes. However, the long-term function of the graft is not ensured and the problem of autoimmunity remains. An interesting alternative is a bioartificial pancreas in which islets are encapsulated. However, the islet environment within such a pancreas still needs to be improved, namely to better preserve islet survival and function.

This project led by Patrick Vermette aims at developing a diabetes drug screening platform based on a novel biomatrix that mimics the 3D environment of pancreatic islets. The team has already determined the appropriate matrix and islet culture conditions, and developed a low-fouling surface on which biomimetic peptides can be applied. Using some of these peptides, they were able to show enhanced islet cell adhesion and even insulin production. This 3D culture system with stable and functionally active pancreatic islets will then be validated as a drug screening platform both *in vitro* and *in vivo* in a bioartificial pancreas. Upon its development, this platform is likely to improve and accelerate novel diabetes drug development and testing.

23. BIOMARKERS TO FOLLOW PANCREATIC BETA-CELL MASS AND FUNCTION IN DIABETES PATIENTS

***completed project**
Investigators: **Eustache Paramithiotis** (Caprion Proteomics Inc.), Marc Prentki (CRCHUM), and Rémi Rabasa-Lhoret (IRCM - Université de Montréal)
• $2.3M from CQDM over 3 years

Pancreatic islets are a central component of diabetes development with about 50% of their function being lost by the time prediabetes is diagnosed. There is thus an urgent need to develop biomarkers that accurately measure ß-cell numbers and function, as well as biomarkers to predict patient response to therapies.

By focusing on blood proteins secreted by normal and dysfunctional pancreatic ß-cell islets, Caprion Proteomics, a leader in proteomics analysis, developed a panel of pancreatic ß-cell biomarkers to follow the function (128 BCF markers) and mass (200 BCM markers) of pancreatic cells in blood samples of diabetes patients. By analyzing the blood of 42 diabetes patients treated with different metformin modalities, Caprion also identified more than 150 treatment efficacy biomarkers (TEM). Validation of the BCF and BCM markers was performed on prediabetic and diabetic patients and led to the identification of a panel of 30 markers which, when used in various combinations, are able to separate clinical cohorts at various stages of disease progression with high (>75%) accuracy.

These findings provided a solid proof of concept demonstrating that identified pancreatic ß-islet and blood biomarkers can effectively help diagnose and monitor diseases as well as predict early response to diabetes treatment. The platform also allowed Caprion to establish important contracts with three (3) major pharmaceutical companies. Moreover, Caprion has raised $30M to establish its own diagnostic division in which these biomarkers are leading assets that are currently being validated through further clinical trials.

24. MINIATURIZED BIOSENSOR FOR CONTINUOUS MONITORING OF MULTIPLE ANALYTES *IN VIVO*

Investigators: **Emanuel Escher**, Vincent Aimez, André Carpentier, Paul Charrette, Michel Grandbois and Éric Marsault (Université de Sherbrooke), Claudine Allen (Université Laval), Didier Leconte (MSBi Valorisation) and Vincent Poitout (Université de Montréal)

This ambitious project was halted due to technical problems that made it impossible to meet objectives and deliverables leading to the development of this technology as expected.

INFECTION & IMMUNITY

25. NOVEL HIGH-THROUGHPUT PLATFORM TO ACCELERATE THE DISCOVERY AND DEVELOPMENT OF NEW VACCINE ANTIGENS BASED ON VIRUS-LIKE PARTICLES (VLPs)

***completed project**

Investigators: **Louis-Philippe Vézina** (Medicago Inc.), Alain Garnier (Université Laval) and Brian Ward (McGill University) ***• $1.8M over 3 years***

VLP*Express*™ is a novel high-throughput technology that accelerates the discovery of new vaccine antigens based on virus-like particles (VLPs), which are protein shells harbouring short strands of the antigens specific to the disease the vaccine is intended to control. Upon transient expression in plant leaves, Medicago can rapidly produce and isolate a high quantity of VLPs (7 viral families have been targeted), doing so ten times faster and operating at a tenth of the cost of existing systems. Because they are mimicking the virus structure, VLPs are rapidly recognized by the body's immune system. Medicago has thus been working actively to develop new products, vaccines and other recombinant proteins against viruses such as the rotavirus, the human papillomavirus (vaccine candidates are in preclinical development) and more recently antibodies to fight emerging diseases or bio-threats such as Ebola.

VLP*Express*™ has been transformational for Medicago. It has allowed the company to reinforce its leadership position, accelerate its development into a fully integrated vaccine company and increase its capacity to develop products and to attract significant partners (e.g. Mitsubishi Tanabe Pharma which acquired the company in 2013, the US and the French governments). Capitalizing on these strategic developments, Medicago announced in May 2015 investments of $245M to transform its installations from a pilot to a full-scale manufacturing plant in Quebec City to commercialize its vaccines. Direct and indirect economic benefits of this new investment are estimated at $461M over the next five years.

26. PINPOINTING CRITICAL DRUG TARGETS FOR AUTOIMMUNE DISEASES

***completed project**

Investigators: **Brent Richards** and Constantin Polychronakos (McGill University) ***• $300k over 2 years***

Autoimmune diseases are a major cause of morbidity and mortality throughout the world. To better understand their causes, Brent Richards used exome sequencing to demonstrate that autoreactive T cells within the inflamed joints of rheumatoid arthritis patients carry de novo somatic mutations that are absent from non-autoreactive T cells circulating in the periphery. They first confirmed the presence of somatic mutations, which are expected to occur within the T cell receptors of auto-reactive T cells. They then identified three de novo copy number changes within the T cells present in the aspirated joint space fluid, but absent from the circulating T cells. These copy number changes were identified on chromosome regions encoding genes implicated in autoimmunity (RAC1, CYTH3, GRID2IP, PMS2CL, SSH3 and PTPRCAP). Single nucleotide polymorphisms which were discordant between the joint space T cells and the circulating T cells were also detected. The identification of such mutations provide evidence suggesting an entirely novel paradigm for the etiology of autoimmunity. More importantly, the results provide new critical drug targets for the pharmaceutical industry. As a result of this CQDM grant, Brent Richards' group was able to secure a competitive grant from Eli Lilly to further pursue this research.

27. SELECTOMICS TO MONITOR AND PREDICT THE EMERGENCE OF RESISTANCE TO ANTIBIOTICS

***completed project**

Investigators: **Michel G. Bergeron**, Jacques Corbeil, Marc Ouellette, Paul H. Roy and Sylvie Trottier (Centre de recherche en infectiologie – CRI – Université Laval) and Maurice Boissinot (GenePOC) ***• $2M over 3 years***

Could the human microflora, normally considered innocuous or beneficial, be contributing to the increased multiple antibiotic resistance seen over the past decades?

To help answer this question, the team of Dr. Bergeron has successfully developed genomic tools to determine how antibiotic exposure alters the gut ecosystem and may trigger the emergence of antibiotic-resistant pathogens upon transfer of genes from the normal gut bacteria to such pathogens. Fecal flora from 18 healthy individuals exposed to antibiotics was collected and members of the aerobic and anaerobic communities of microbes were cultured. The metagenome of both cultured and uncultured gut microbiota was analysed (close to 1,600 billion nucleotides) to identify genes (1,760 sequence types) and mobile genetic elements (2,895 sequence types) involved in antibiotic resistance. The research team also derived 2,760 gut microbiota cultures which can be used to screen, isolate, and characterize bacterial species that are resistant to antibiotic drugs early in the drug development process.

The results of this project show the importance of the gut microflora in antibiotic resistance and are thus pivotal in understanding the effects of antibiotics on microbiota, quantifying the presence of resistance genes and mobile genetic elements, identifying new resistance genes, monitoring and predicting the resistance of new drugs, and assessing the activity of antibiotic compounds against a wide spectrum of resistance determinants, which will ultimately be used to develop new and more potent antimicrobial treatments.

DRUG DELIVERY

28. GENE THERAPY: DNA AT THE SERVICE OF EYE DISEASES

Investigators: **Elizabeth M. Simpson** (Centre for Molecular Medicine and Therapeutics, University of British Columbia) and Adriana Di Polo (Research Centre of the Centre hospitalier de l'Université de Montréal (CHUM))
Date of initiation: May 2015 ***• $1.5M over 3 years in collaboration with Brain Canada***

Diseases of the eye, sometimes leading to blindness, are excellent targets for gene-based therapies, where a functional gene is inserted into a patient's cells in order to produce the protein that can cure or prevent a disease. Unfortunately, this approach has not delivered all its promises yet.

The team of Elizabeth M. Simpson argues that, with better promoters, gene therapy would become safer and more effective. However, a major challenge is that normal human genes have very long and complex promoters, whereas gene therapy needs very small promoters or MiniPromoters.

In this innovative approach, Professor Simpson will use a large-scale genome-wide approach and engineer 45 human MiniPromoters associated with restricted eye expression. The MiniPromoters will drive the expression of GFP (Green Fluorescent Protein), which will be easily detectable. These MiniPromoters will be inserted in adeno-associated viruses (AAVs) to allow their expression in different animal models. These MiniPromoters will be tested in mice to carefully map their pattern of expression during development, as well as in adults (injection in eyes). The three best MiniPromoters (based on specificity of expression) will then be injected in monkeys' eyes to further ensure restricted expression. Such experiments will identify which MiniPromoters could be used in gene therapy. The application of this work is when the GFP marker is replaced by the gene affected in an eye disease. The administered genes will then be translated into useful therapeutic proteins for various eye diseases including loss of vision and blindness.

29. MAGNETICALLY GUIDED DRUG DELIVERY PLATFORM FOR THE TREATMENT OF COLORECTAL CANCER

Investigators: **Sylvain Martel** (Polytechnique Montréal), Michael Atkin (Syzent Partners), Gerald Batist, Nicole Beauchemin, Danuta Radzioch, Maryam Tabrizian and Te Vuong (McGill University), Louis Gaboury and Michel Lafleur (Université de Montréal)
Date of initiation: September 2011 ***• $1.9M over 3 years***

Cancers are treated today with a combination of chemo-therapeutic drugs, surgery and radiation. Chemotherapy is almost invariably dosed intravenously, coming into contact with healthy cells, resulting in important side effects.

The project led by Sylvain Martel proposes a disruptive approach using drug-loaded magnetotactic bacteria (MC-1) whose flagella will propel them directly to tumour sites. These bacteria travel through small blood vessels and are directed by an external magnetic field controlled by a computer. The project aims at a proof-of-concept in colorectal cancer models using SN-38-encapsulated liposomes (a topoisomerase I inhibitor). The team has already shown the feasibility of this approach by injecting human colorectal cancer cells in mice and demonstrated a significant decrease in tumour volume and the presence of fibrotic tissue with extensive necrosis upon guiding MC-1/SN-38 bacteria to the tumour site. This platform, which could be adapted to many different anticancer agents and types of tumours, will help increase the efficacy and reduce the side effects of anticancer drugs.

30. NOVEL LASER-ASSISTED INTRAOCULAR DRUG DELIVERY SYSTEM CARRIED BY GOLD NANOPARTICLES

Investigators: **Michel Meunier** (Polytechnique Montréal), Przemyslaw Sapieha and Santiago Costantino (Université de Montréal)
Date of initiation: December 2013 ***• $300k over 2 years***

Retinal degenerative diseases, such as age-related macular degeneration and glaucoma, are the leading causes of vision loss and affect tens of millions of individuals in the world. Developing a safe and effective drug delivery system for retinal ganglion cells (RGCs) and retinal pigment epithelium (RPE) cells to address the current void in retinal drug delivery systems would open novel therapeutic avenues.

To address this limitation, the team is developing a laser-based delivery platform for retinal cells using ultrafast laser irradiation of gold nanoparticles in the presence of siRNAs. By specifically tagging these nanoparticles, they can selectively target retinal pigment epithelium (RPE) or retinal ganglion (RGC) cells. The bioconjugated gold nanoparticles will be tested *in vivo*, and as a proof of concept, anti-VEGF siRNA will be delivered to RGC cells (involved in glaucoma), while anti-apoptotic siRNA (targeting c-Jun or Apaf-1) will be introduced in RPE cells (involved in age-related macular degeneration). The laser-mediated siRNA delivery in the presence of conjugated gold nanoparticles developed in this project will open novel therapeutic avenues for the delivery of silencing RNAs, therapeutic genes and eventually small molecules to the back of the eye, but could also be applied to cancer, neurodegenerative diseases and other disorders.

IMAGING TECHNOLOGIES

31. DRUG DELIVERY PLATFORM FOR SILENCING RNAs USING EXOSOMES

Investigator: **Derrick Gibbings** (University of Ottawa)
Date of initiation: June 2015 • ***$300k over 2 years in collaboration with OCE***

Silencing RNAs (siRNAs) are a new type of molecule that could inhibit virtually any gene. Because most diseases could benefit from shutting-down the action of a specific protein encoded by its gene, it is suggested that siRNAs could be used to treat virtually any diseases. Unfortunately, the ability to specifically deliver siRNAs into the tissues and organs where they are needed has prevented us so far to use them as drugs.

Derrick Gibbings' team may have discovered a novel mechanism to selectively introduce any therapeutic siRNA into exosomes (tiny vesicles that can transport siRNAs between cells) and use them as delivery vehicles. More specifically, they will optimize their technology of siRNAs so that different cell types (immature dendritic cells and embryonic stem cells) can robustly package the modified siRNA into exosomes. The scientists will then modify the exosomes so that they can be directed to specific tissues other than liver. The immunogenicity and oncogenicity of these loaded exosomes will be assessed upon injection in mouse models. The researchers will then test if the siRNAs are active (inhibiting gene expression) in the cells where they have been delivered. In the drug development process, this technology could be used to deliver new drugs (siRNAs) specifically to the disease sites, thus avoiding side effects. This could thus enable the treatment of many previously untreatable diseases with silencing RNAs.

32. PulmoBind: BIOMARKERS FOR PULMONARY HYPERTENSION

Investigators: **Jocelyn Dupuis** and François Harel (Montreal Heart Institute), Alain Fournier (INRS – Institut Armand Frappier)
Date of initiation: September 2011 • ***$2.8M over 3 years***

Pulmonary arterial hypertension (PAH) is a frequent condition causing a progressive loss of blood vessels in the lungs. It causes substantial disability with a progressive increase in shortness of breath and can sometimes lead to death. There is currently no cure for PAH and the development of effective drugs is complicated by the lack of easy tests to detect the disease at an early stage and to follow its progression.

The project led by Dr. Jocelyn Dupuis provided the first safe, sensitive and non-invasive molecular imaging agent for early diagnosis of PAH. The PulmoBind clinical diagnostic kit (based on a derivative of human adrenomedulin) was validated in Phase I (20 healthy subjects) and Phase II (15 healthy subjects compared to 30 PAH subjects) clinical trials. The researchers demonstrated that PulmoBind is safe and showed that PulmoBind SPECT analysis is very abnormal in PAH patients.

PulmoBind has thus the potential to replace the existing outcome measure (6-minute walk test) for early diagnosis and to monitor treatment efficacy in clinical trials.

Following this success and in collaboration with Merck, the Montreal Heart Institute is currently developing a PET-imaging version of PulmoBind called DHF-17, which is already working in an animal model. The technology was licensed to PulmoScience Inc. for commercialization.

33. MONITORING THE SIGNALING PATHWAYS OF GPCRs IN LIVING ANIMALS

Investigators: **Michel Bouvier** (Institut de Recherche en Immunologie et en Cancérologie de l'Université de Montréal), **Brigitte Kieffer** (Institut de Génétique et de Biologie Moléculaire et Cellulaire -IGBMC- de Strasbourg), and Pascal Neuville (Domain Therapeutics)
Date of initiation: November 2012 • ***$529k and €383k over 3 years in collaboration with French partners***

Because they are involved in so many physiological processes, G protein-coupled receptors (GPCRs) are the site of action for about 40% of marketed drugs and remain a prime target for the development of new therapeutics. To test the activity of drug candidates, understanding their action on their target in living animals is essential. However, this goal represents a true challenge due to the complexity of GPCR signaling in normal physiology and disease states.

To tackle this challenge, the team has combined its expertise in GPCR signaling and in vivo imaging to generate new genetically engineered knock-in mice that allow the direct observation of drug action on specific GPCRs (GPR88, CXCR7, mGLUR5 and MOR), effectors (βarrestin-2, Gαi(2), Gαq, Gγ(2)) and signaling events through newly developed microscopy imaging techniques using fluorescent and bioluminescent resonance energy transfer (F/BRET) sensors. This platform will improve preclinical GPCR drug discovery programs for screening desirable from undesirable signaling effects and ultimately developing drugs with greater therapeutic efficacy and fewer side effects.

34. FLUORESCENCE LIFETIME IMAGING SYSTEM TO STUDY PROTEIN-PROTEIN INTERACTIONS IN LIVE CELLS

Investigators: **Ozzy Mermut** and Pascal Gallant (Institut national d'optique), **David W. Andrews** (Sunnybrook Research Institute), and Qiyin Fang (McMaster University)
Date of initiation: September 2014 • ***$475k over 3 years in collaboration with OCE***

Early in the drug discovery process, screening tests are used to pinpoint drug candidates that will have a potent effect on the target pathology. Since many relevant targets can only be affected by drug candidates acting within cells, screening of living cells is conducted with sophisticated automated microscopy systems (high-content screening or HCS). However, there are limitations to these systems, notably for resolving and studying protein-protein interactions (PPIs), a class of in-cell biomedical phenomena that are very relevant to anticancer and other drug development pipelines.

With this project, the researchers are developing a novel prototype of an HCS attachment that could be added to most high quality commercial fluorescence microscopes to detect PPIs by taking photos of fluorescence proteins in living cells. Called Fluorescence Lifetime Imaging (FLIM), their confocal-based instrument will provide high resolution and high speed imaging (512 x 512 pixels in less than 10 seconds) of PPIs in order to detect disruption by drug candidates. Their system will first be validated using the Bcl-2 family of proteins that regulate apoptosis but could also be used to accelerate new drug development targeting a wide variety of other PPIs. The prototype developed during this project is thus likely to meet the requirements of pharmaceutical companies in terms of affordability and usefulness in a screening context.

BIOLOGICS

35. INCREASING THE ORAL BIOAVAILABILITY OF MACROCYCLES

Investigators: **Jeffrey Coull** (Encycle Therapeutics) and Andrei Yudin (University of Toronto)
Date of initiation: March 2015 • ***$838k for 1 year in collaboration with MaRS Innovation and Encycle Therapeutics***

Building on the successful development of its macrocycle platform funded by CQDM, Encycle Therapeutics is now working to better understand the chemical properties required by the nacellins to make them orally bioavailable. More specifically, Encycle is adding more than 350 new nacellins to the original library and is developing an algorithm that will predict which properties of these small circular peptide-like molecules are responsible for their oral bioavailability.

The great versatility of nacellins allows them to enter the cells and interact with targeted proteins hitherto untouchable. Nacellins are thus inhibiting protein-protein interactions and thus interfere with the activity of such protein complexes. It is therefore not surprising that large pharmaceutical companies are interested in nacellins which they consider as future key-drugs for the treatment of several diseases. Encycle Therapeutics has recently raised a seed financing round of $3M, led by Takeda Ventures and is in advanced discussions for series A funding of $15M.

36. A RAPID, SENSITIVE AND SPECIFIC ASSAY FOR DETECTING IMMUNOGENICITY OF THERAPEUTIC BIOLOGICS

Investigators: **Patrick Vermette** and Tamas Fülöp (Université de Sherbrooke)
Date of initiation: December 2013 • ***$300k over 2 years***

Immunogenicity, defined as the ability of a particular substance to provoke an immune response in the body, can be a problem when treating patients using biologics, as it can result in anti-drug antibody (ADA) production. ADA can reduce the bioavailability of the biologics and cause adverse clinical events.

The researchers combined a quartz crystal microbalance (QCM) technique with low-fouling substrates bearing ligands to specifically detect ADAs and predict cellular-mediated immunological mechanisms in complex biological fluids such as blood. The team demonstrated that ADAs from rabbits immunized with Enbrel® were successfully detected using the QCM instrument they developed, with a sensitivity similar to an ELISA. The researchers have also developed an assay to detect lymphocyte activation from biologics immobilized on their low-fouling surfaces using flow cytometry. This new technology opens the door to personalized medicine for immunogenicity detection, which will involve exposing whole blood from individuals to biologics immobilized on low-fouling surfaces to detect putative adverse ADA production.

37. NEXT GENERATION TECHNOLOGY TO INCREASE HALF-LIFE OF SMALL BIOLOGICS

Investigators: **Traian Sulea,** Jason Baardsnes and Maureen D. O'Connor-McCourt (National Research Council Canada)
Date of initiation: December 2013 ***• $489k over 2 years in collaboration with NRC***

The efficacy of biologics as therapeutics is strongly dictated by their circulating half-life and tissue penetration. Their hydrodynamic radius affects both these properties, in that increasing their molecular size will increase their half-life but will decrease their tissue penetration. Hence, many promising small-size biologics are unviable as clinical candidates despite their excellent potential in terms of on-target efficacy, off-target selectivity and tissue penetration.

The team is developing the novel RecyTag platform to design highly effective small biologics with increased circulation times through conjugation with low-molecular-weight molecules targeting the FcRn recycling receptor. The researchers will identify a few small molecules from a newly selected drug-like compound library enriched for pH-dependent FcRn-binding.

These molecules will then be conjugated to three biologics having short half-lives in order to stabilize them (a small fluorescent protein for easy visualization and two proteins targeting either the transforming growth factor beta or the epidermal growth factor receptor). The platform will be developed through *in silico* and *in vitro* screening and validated with pharmacokinetic and efficacy testing. This technology aims to maximize target tissue bioavailability, potentially improving the efficacy of novel and existing biologics, hence opening major new markets.

38. IMPROVED CHEMISTRY PLATFORM FOR THE RAPID SYNTHESIS OF UNIQUE MACROCYCLES AS PROTEIN-PROTEIN INTERACTION PROBES

***completed project**
Investigators: **Andrei Yudin** (University of Toronto/Encycle Therapeutics Inc.) and **Éric Marsault** (Université de Sherbrooke) ***• $1M over 2 years in collaboration with MaRS Innovation***

This project successfully developed a powerful chemistry platform employing aziridine aldehyde that allowed for a more efficient design and synthesis of unique macrocycles – cyclic peptides or nacellins – with enhanced potential for cell permeability and oral bioavailability.

A library of more than 1,400 nacellins was generated and comprehensive ADME and PK evaluations were performed on representative scaffolds from the library. Ultimately, this unique technology will enable the development of therapeutics with an ability to not only inhibit extracellular proteins following oral administration, but also to target the hitherto "undruggable" intracellular protein-protein interactions.

This project led to the creation of Encycle Therapeutics, which is dedicated to the development of nacellins as new medicines. Mentors from CQDM's pharmaceutical members have provided significant contributions to this research project and are now screening the library against a limited number of therapeutic targets of their choice. The discovery of "hits" from this screening effort would open the door to long-term strategic partnerships between them and Encycle.

SCREENING PLATFORMS

39. 3D LIVER TISSUE MODELS TO ASSESS TOXIC EFFECTS OF DRUGS

Investigators: **Craig Simmons**, Michael Sefton, Denis Grant and M. Dean Chamberlain (University of Toronto)
Date of initiation: June 2015 ***• $300k over 2 years in collaboration with OCE***

Poor efficacy and unpredictable toxic effects are the leading causes for removal of a drug from the market. Many drugs act unpredictably in patients because preclinical studies poorly mimic what will happen in humans. Since many drugs are metabolized in the liver, improved liver models are thus essential in order to assess the toxicity of new compounds.

To meet this need, Craig Simmons' team has developed three-dimensional vascularized liver microtissues that will be incorporated in an easy-to-use microfluidic platform. This new and improved liver model similar to native human liver tissue will be unique in its compatibility with standard laboratory equipment and the biopharmaceutical industry R&D processes, ensuring ease of implementation with minimal time and effort.

In this project, the researchers will validate their 3D liver microfluidic system by assessing long-term liver viability, metabolic function, and toxicity in response to test compounds with known effects. The team will then test the predictability and usefulness of their platform by showing the adverse metabolic and toxic effects of compounds that previously passed *in vitro* testing but failed in preclinical trials. At project completion, they will deliver a new best-in-class model of human liver that is expected to decrease the time and cost associated with drug development by identifying ineffective and toxic drugs much earlier in the drug development process (during the hit-to-lead and lead optimization steps) than is possible with current methods. This platform thus represents a game-changer as it will be, for the time being, the most predictive *in vitro* liver model available and directly transferable to end users for immediate impact.

40. DEVELOPMENT OF INNERVATED, VASCULARIZED AND IMMUNOCOMPETENT TISSUE-ENGINEERED HUMAN SKIN FOR DRUG SCREENING

Investigators: **Francois Berthod** (Université Laval), **Vincent Flacher** and Christian Mueller (CNRS), Dan Lipsker (CHU Strasbourg) and Roxane Pouliot (Université Laval)
Date of initiation: August 2015 ***• $552k and 341k€ over 3 years in collaboration with Alsace BioValley and Lyonbiopole***

One of the major concerns in the development of a new compound by the chemical, pharmaceutical or cosmetic industries is to assess its ability to induce cutaneous allergic reactions. Indeed, the industry must be able to predict such risk and classify it before commercialization of new molecules. To date, these tests are performed on animals, raising both ethical and reliability issues.

The goal of this project is thus to develop a very innovative *in vitro* drug screening platform, based on a tissue-engineered human skin model. This reconstructed tissue will combine for the first time immune cells, a sensory nerve network and microvascular vessels, interacting with each other in order to reproduce *in vitro*, and with unprecedented sensitivity, an immunocompetent skin with properties as close as possible to normal skin.

At the end of this project, the research team will have provided a very relevant HTS sensitivity test that will surpass current preclinical testing and greatly facilitate the characterization of the mechanism of action of new drugs on human skin cells in real time. In addition, it will be possible to accurately mimic skin diseases such as psoriasis and lupus erythematosus, and thus to screen novel molecules for their therapeutic potential.

41. NEW BIOSENSORS FOR GPCR MOLECULAR SIGNATURE TO BETTER UNDERSTAND THE EFFECTS OF DRUGS

***completed project**
Investigators: **Michel Bouvier** (Institut de Recherche en Immunologie et Cancérologie de l'Université de Montréal), Terence Hébert and Stéphane Laporte (McGill University), Richard Leduc (Université de Sherbrooke), Graciela Pineyro (CHU Sainte-Justine - Université de Montréal), Jean-Claude Tardif and Eric Thorin (Montreal Heart Institute) ***• $1.8M over 3 years***

G protein-coupled receptors (GPCRs) form the largest family of cell surface receptors involved in signal transduction of most hormones and transmitters. It follows that drugs targeting GPCRs represent close to 40% of all drugs on the market today. Recent discoveries about their mode of action pave the way for the development of an even greater number of more specific therapeutics in many clinical indications. However, the necessary tools to study their intricate signaling networks are lacking.

This project has delivered a high-throughput drug screening toolkit consisting of 37 cell-based biosensors to monitor the various signaling pathways engaged by GPCRs upon ligand binding. The technology, based on bioluminescence resonance energy transfer (BRET), provides a direct measure of molecular activation and interactions inside living cells. This approach pioneers a timely shift from the current single functional assays screening approach to a rapid parallel multidimensional platform for GPCR screens, thus allowing to predict efficacy as well as undesirable side-effects of drug candidates.

The technology has already been integrated in CQDM pharma partners' internal research and has led to a meaningful partnership with Pfizer who has committed a substantial additional amount to develop specific signaling signatures. Both Pfizer and Merck in-licensed the technology for their drug discovery programs. In 2013, the technology was licensed-in by Domain Therapeutics-France who created a subsidiary in Montreal called Domain Therapeutics North America (DTNA) to exploit the platform *BioSens-All™* on a fee-for-service basis. DTNA has already executed service contracts with more than 15 pharma organizations, biotech and academic groups in North America, Europe and Japan.

42. ZEBRAFISH HTS PLATFORM FOR NUCLEAR RECEPTOR-RELATED DRUG DISCOVERY AND PATHWAY ELUCIDATION

Investigators: **Henry Krause** (University of Toronto), Vincent Giguère (McGill University) and Jens Tiefenbach (InDanio Biosciences)
Date of initiation: July 2015 ***• $1M over 2.5 years in collaboration with CIHR and inDanio***

Building on the success of the first project, the team is now completing its zebrafish platform to study the 48 human nuclear receptors (NRs) as well as six (6) epigenetic-regulating cofactors, providing highly cost-effective, accurate HTS for NR-targeted drug discovery. Embryos from these fish can be collected by the thousands and screened rapidly against an equal number of drug candidates. Active compounds (and eventually drugs) cause the fish to glow green in responding tissues, and directly acting molecules or metabolites can then be co-purified and identified. *InDanio* is already using this platform to establish its own pipeline by identifying new hits from a library that contains existing, potential and off-patent drugs, as well as natural compounds and 'medically friendly' compounds assembled by the Canadian Centre for Drug Research and Development (CDRD).

With its 54 transgenic zebrafish lines, this technology has the potential to replace cell-based assays for nuclear receptor drug screening, reducing the amount of preclinical testing, providing greater predictability of target and tissue specificity, as well as better addressing ADME challenges. It thus brings to the pharmaceutical industry an innovative approach to drug discovery and genome-wide pathway analysis for the benefit of patients affected by the many diseases involving nuclear receptors.

43. MAMMALIAN MEMBRANE TWO HYBRID (MAMTH) AS AN INNOVATIVE TECHNOLOGY FOR DRUG DISCOVERY

Investigator: **Igor Stagljar** (University of Toronto)
Date of initiation: June 2015 ***• $300k over 2 years in collaboration with OCE***

Membrane proteins, representing approximately one-third of all proteins in a cell, interact with each other and are responsible for a variety of processes, making them attractive therapeutic targets for many diseases such as hypertension, diabetes, neurological disorders and various cancers. In fact, membrane proteins represent 60% of all clinical drug targets, however, they are still extremely difficult to study because of their biochemical complexity, and therefore could not be studied extensively using any available technology. Igor Stagljar and his team have recently developed a novel platform called Mammalian Membrane Two Hybrid (MaMTH) to study the interactions of any mammalian membrane protein *in vivo*, as well as understand how such protein interactions respond to various therapeutic compounds directly in their natural cellular context. The two-hybrid screen is based on disrupting protein-protein interactions between a "bait" and a "prey" of therapeutic importance. Using the CRISPR/Cas9 and Flp-In TREx systems, the research team will tag (using luciferase) a set of selected human membrane proteins.

To establish the proof-of-concept, the team will screen a library of more than 200,000 small molecules to identify those that can disrupt interactions between EGFR and its protein partners. MaMTH will thus become a powerful drug discovery assay for context-dependent high-throughput identification of lead molecules that inhibit protein-protein interactions of any human membrane protein of therapeutic interest.

44. HIGH-THROUGHPUT SCREENING PLATFORM FOR RAPID DISCOVERY OF NOVEL ANTI HERPETIC DRUGS

***completed project**
Investigators: **Matthias Götte**, McGill University and Guy Boivin, Université Laval ***• $1.3M over 3 years***

Infection with herpes viruses is associated with important human diseases including the development of cancers. Patients receiving organ transplants and having immune deficiencies are particularly sensitive to such infections. These patients are treated with antiviral agents; however, the approved drugs are often associated with severe side effects and the development of resistance can compromise therapy. There is thus an urgent need to discover novel antiviral agents that target the various members of the herpes virus family.

The team of Matthias Götte has developed a sensitive high throughput platform with a phage-based approach targeting the common portions of herpes virus DNA polymerases. Their phage/virus chimeric polymerases can be seen as herpesvirus orthologs. These enzymes are produced in high quantities to facilitate drug discovery. They also validated antiviral drug susceptibility tests for Epstein-Barr virus (EBV), human herpesvirus 6 and 8 (HHV-6 and HHV-8) using real-time PCR-based assays as well as antiviral drug toxicity assays on relevant cell lines. This platform has the potential to screen at low costs for novel antivirals with broad-spectrum activity against all eight members of the herpes virus family with the ultimate goal to improve treatment of infection with these pathogens. The technology has been integrated within the R&D process of at least one of CQDM's pharmaceutical members.

45. PLATFORM FOR *IN VIVO* NUCLEAR RECEPTOR DRUG SCREENING AND THE DISCOVERY OF NEW PATHWAYS IN METABOLIC DISEASES AND CANCER

Investigators: **Vincent Giguère** (McGill University) and **Henry Krause** (InDanio Biosciences)
Date of initiation: August 2013 ***• $550k over 3 years in collaboration with OCE***

Nuclear receptors (NRs) are a family of proteins that control processes such as metabolism, growth and behaviour. They are also implicated in diseases such as diabetes, Parkinson's, Alzheimer's and cancer. Conversely, nuclear receptors represent one of the main targets of existing drugs. However, mainly due to a lack of appropriate screening platforms, there has been a massive decline in recent NR-directed drug discovery.

In order to circumvent this problem, Henry Krause first developed the Ligand Trap System (LTS), a unique, highly efficient high-throughput live animal screening platform targeting nuclear receptors. Using transgenic zebrafish, the researchers can then visualize endogenous ligands and potential drug activity three-dimensionally, and then isolate these new ligands, active drugs or metabolites from the responding tissues. These fish and their responses can also be used to identify and evaluate new disease pathways. The platform was validated by identifying new ligands for peroxisome proliferator-activated receptors (PPARs), retinoid-related orphan receptors (RORs) and for farnesoid-X transgenic receptor (FXR) for metabolic diseases and cancer indications. This platform was instrumental in the creation of *InDanio*, a service-oriented CRO offering high-throughput *in vivo* screening of new chemical entities targeting the nuclear receptor protein family.

46. FLASHWALK MAPPING: A STEP-BY-STEP APPROACH TO GPCR CONFORMATION CARTOGRAPHY

***completed project**
Investigators: **Terence Hébert** (McGill University), Sylvain Chemtob (CHU Sainte-Justine - Université de Montréal), Audrey Claing and William Lubell (Université de Montréal) and Stéphane Laporte (MUHC Royal Victoria Hospital)
• $300k over 2 years

G protein-coupled receptors (GPCRs) are the targets of a large number of drugs used to treat human diseases. GPCRs are extremely dynamic with respect to how they interact with their natural activators and the drugs which target them as well as with their partners which effect changes in cell function downstream.

The "FIAsHwalk mapping" strategy developed by Terence Hébert and his team is an innovative and easy-to-follow approach that uses fluorescent and bioluminescent reporters to visualize conformational dynamics of receptors to better understand the interactions between drugs and their target GPCRs. Using the angiotensin II (AT1R) and prostaglandin F (FP) receptors as proof of concept, the team showed that receptor reporters produce unique FIAsHwalk signatures or "heat maps" that characterize their interactions with molecular or protein partners. Moreover, FIAsHwalk maps can be correlated with various phenotypic measures of drug effects, including signaling pathways, cellular changes as well as *in vivo* data. The technology thus allows the identification of GPCR modulators, thereby enabling the design of more effective GPCR-based therapeutics.

47. MONITORING CONFORMATIONAL CHANGES OF CHANNEL PROTEINS: A NOVEL APPROACH FOR RAPID SCREENING OF ION CHANNEL HITS

***completed project**
Investigators: **Graciela Pineyro** (CHU Sainte-Justine - Université de Montréal) and Terence Hébert (McGill University) ***• $300k over 2 years***

Ion channels are involved in numerous physiological functions; it is thus not surprising that these channels can be used as drug targets for treating a wide range of pathological conditions. However, despite considerable efforts, channel-targeted drug discovery has been hampered by the absence of adequate tools to mine large libraries of compounds in search of drugs that can influence channel function.

In this project the researchers have developed an innovative approach that allows real-time assessments of ion-channel conformational responses and structural rearrangements of channel subunits upon binding with different ligands. Using the highly sensitive bioluminescence resonance energy transfer (BRET) technology, the researchers have generated 20 BRET constructs of different Kir3 ion channel subunits. They validated their system by showing the correlation of dose response curves generated in BRET assays with ion flux assays, commonly used by the industry to identify channel modulators. The fact that the biosensors show conformational changes in the channel allows them to respond to all forms of ligands, not merely activating ligands. The Kir biosensors constructed in this study were also shown to be able to discern interactions with known antagonists of Kir3 channels, which further increases their utility as a screening device for compound libraries.

These tools offer the opportunity to develop a new generation of channel modulators with novel mechanisms of action, and could even predict phenotypic responses from conformational profiles in very early stages of drug development. The technology may also be adapted for other multimeric channels such as the ion channel gated TRPV and P2X, as well as voltage-gated channels (K+ or Ca+).

BIOINFORMATICS

48. COMPUTATIONAL AND MACHINE LEARNING APPROACHES TO IMPROVE DESIGN AND SCREENING OF HIGH BIOACTIVITY PEPTIDES FOR DRUG DISCOVERY

Investigators: **Jacques Corbeil**, François Laviolette, Éric Biron, Mario Marchand, Sylvain Moineau and Adnane Sellam (Université Laval), Mike Tyers (Université de Montréal) and Carlos Sosa (Cray Inc.)
Date of initiation: December 2014 ***• $1.5M over 3 years***

New techniques in machine learning, using special algorithms, can predict if a compound could be efficacious and reduce the cost associated with the drug development process.

By combining their expertise, Jacques Corbeil's team members will use state-of-the-art machine learning algorithms to improve virtual screening of combinatorial linear and cyclic peptide libraries. The researchers will synthesize and assess the activity of millions of peptides against important human pathogens such as *S. aureus* (bacterial), C. *albicans* (fungal) and HIV-1 (viral). Some of these peptides will inhibit protein-protein interactions (PPIs) essential for the life of the pathogens, and nanopore optical interferometry, a new technology that measures biomolecular interactions, will be used to assess their anti-pathogenic activities. The sequences of the best hundred inhibitory peptides will be entered in a multi-cycle feedback approach combining machine learning screening and informed combinatorial chemistry to further improve the properties of these peptides. In other words, the peptides' activity will improve at each iterative cycle. Disrupting protein-protein interactions is becoming one of the best approaches to treat many diseases. This project is thus laying the foundation for a strategy to ultimately develop a peptidomimetic learning algorithm that will identify new and improved peptide drugs for many other therapeutic indications including neurodegenerative diseases and cancer.

49. *IN SILICO* PLATFORM TO INCREASE THE AFFINITY OF THERAPEUTIC ANTIBODIES

***completed project**
Investigators: **Enrico Purisima**, Yves Durocher and Maureen O'Connor-McCourt (National Research Council Canada)
• $300k over 2 years

The development of antibodies to disrupt vital functions of cancer cells is becoming an important strategy in cancer therapy but is a painstaking and haphazard process.

Enrico Purisima and his team developed and validated the innovative ADAPT (Assisted Design of Antibody and Protein Therapeutics) platform to rapidly design antibodies with optimal binding characteristics to a specific antigen. ADAPT interleaves *in silico* directed evolution of the antibody sequence with experimental validation to rapidly zero in on combinations of mutations that are likely to enhance binding affinity. As a proof of concept, the investigators sought to enhance the affinity of the bH1 antibody, which harbours modest affinity (46 nM) for VEGF-A, a protein that stimulates the growth of blood vessels, and which exhibits somewhat stronger affinity (3nM) for HER2, a protein associated with many types of cancer. In both cases, ADAPT achieved impressive improvements in binding affinity after testing only 20 to 30 designed mutant antibodies, almost all of which showed various levels of enhanced affinity. The most potent mutants had a binding affinity of 0.46 nM against VEGF-A (a 100-fold enhancement) and 0.066 nM against HER2 (a 44-fold enhancement).

The efficiency and ease of use of the platform makes ADAPT a valuable tool for antibody design. Given the structure of any antibody-antigen complex, this technology could be used to enhance the binding affinity and has thus implications in all diagnostic and therapeutic fields where antibodies are used, including cancer, rheumatoid arthritis, multiple sclerosis and others.

50. POWERFUL BIOINFORMATICS TOOL FOR RATIONAL AND SELECTIVE DRUG DESIGN

***completed project**
Investigator: **Rafael Najmanovich** (University of Sherbrooke) ***• $300k over 2 years***

While drugs work by modulating the function of target proteins, other proteins may also be affected due to similarities between their binding sites, resulting in undesirable side effects. Detecting such similarities can lead to the prevention of side effects and be used to develop multi-functional drugs that can purposely interact with more than one target.

Rafael Najmanovich has developed IsoMIF, a robust computational software to analyze and calculate molecular interaction fields (MIFs) to identify binding site similarities between receptors and potential off-family cross-reactivity, thus helping to maximize drug specificity and selectivity.

IsoMIF was successfully validated using a subset of the high-quality dataset of inhibition profiles of 224 kinases against 369 inhibitors obtained from the Structural Genomics Consortium (SGC). Interestingly, IsoMIF can detect binding site similarities that could not be predicted based on either sequence or protein folding similarities. Moreover, Professor Najmanovich has created a dataset of human proteins bound to purine-containing ligands (human purinome) to be used in the detection of potential cross-reactivity targets based on the detection of IsoMIF similarities. The bioinformatics tool has thus wide applications in rational drug design and to predict binding cross-reactivity.

DISCOVERY & SCREENING

- Signaling by GPCRs (biosensors, animal models), nuclear receptors (zebrafish) and ion channels (biosensors)
- Detecting signaling in neurons
- Library of macrocycles
- Imaging and targeting protein-protein interactions
- Cancer biomarkers
- Screening anti-aggregation compounds and antivirals
- Tissue engineering
- Brain molecular imaging
- VLP vaccine antigens

TARGET IDENTIFICATION

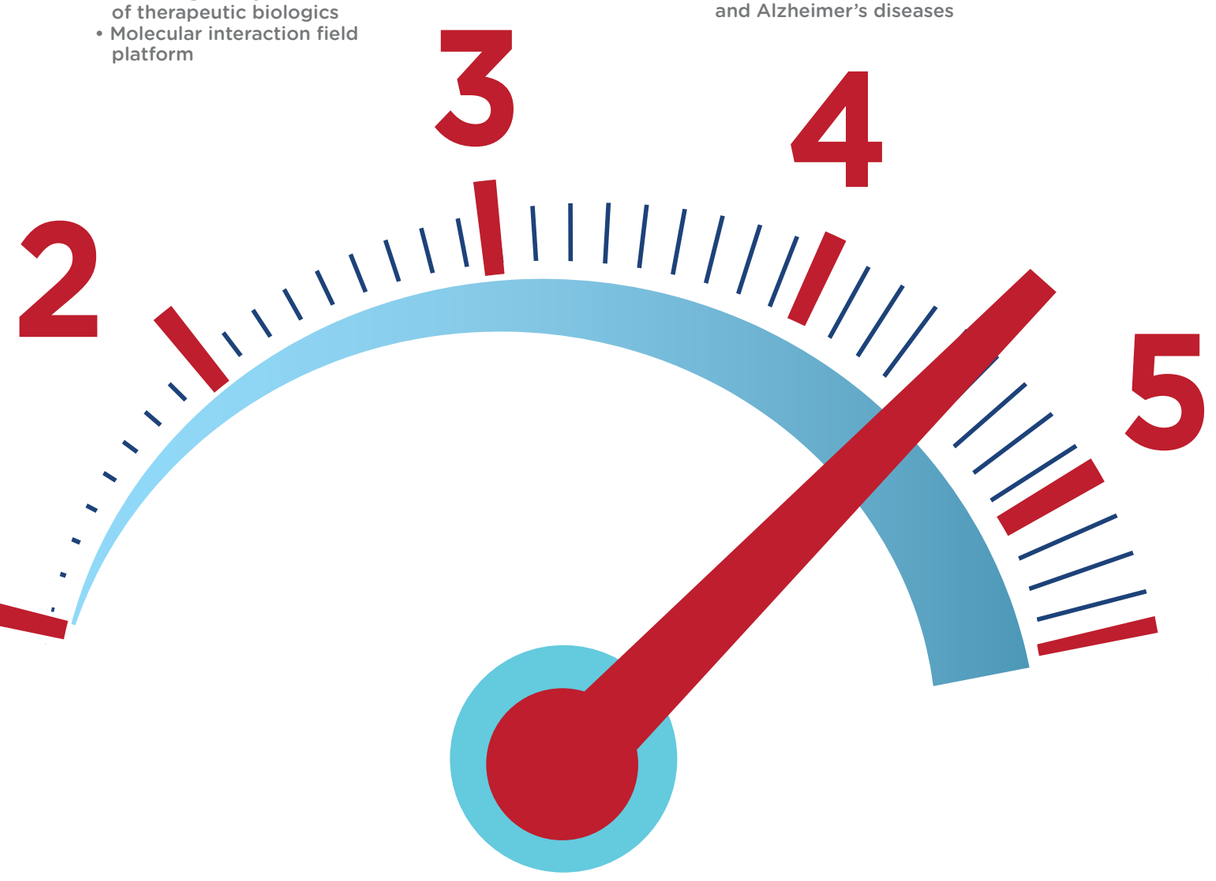
- Synthetic lethality in oncology
- Genetic interactions
- T cell somatic mutations in inflammatory diseases

LEAD OPTIMIZATION

- Developing better mAbs, therapeutic peptides and small biologics
- Immunogenicity detection of therapeutic biologics
- Molecular interaction field platform

PRECLINICAL STUDIES

- Animal models of Parkinson's and Alzheimer's diseases



CLINICAL DEVELOPMENT

- Biomarkers (ERG) for psychiatric disorders, degenerative diseases (AZ, PD), diabetes, pulmonary hypertension, neuroendocrine tumours and breast cancer
- Resistance to antibiotics
- Magnetic guided drug delivery to colon cancer
- Delivering siRNA in exosomes
- Drug delivery to the eyes: nanoparticles and specific promoters
- Personalizing treatments for ovarian and other cancers
- Crossing the blood-brain barrier

6 FDA MARKET

IMPACT OF CQDM'S PROJECTS

ON EVERY STEPS TOWARD THE DRUG DEVELOPMENT PROCESS

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