CQDM/ Brain Canada/ OBI "Focus on Brain" Program

List of Funded Projects

Team Leader and Members	Application Title
Jean-Paul Soucy (McGill University), Frederic Lesage (École Polytechnique of 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.)	Non Invasive Identification of Aβ Plaques in Human Retina for the Diagnosis of Alzheimer's disease
Elizabeth Simpson (University of British Columbia), Adriana Di Polo (Research Centre of the Centre Hospitalier de l'Université de Montréal)	Human MiniPromoters for Restricted Expression of Ocular Gene Therapy
Rob Hutchison and Reinhard Gabathuler (biOasis Technologies Inc.), Danica Stanimirovic (National Research Council Canada), Brigitte Guérin, Roger Lecomte and David Fortin (Université de Sherbrooke)	'Best in Class' Platform for Blood Brain Barrier Delivery of Therapeutics
Janusz Pawliszyn (University of Waterloo), Dajana Vuckovic (Concordia University) and Clement Hamani (Centre for Addiction and Mental Health)	Solid phase microextraction-based integrated platform for untargeted and targeted in vivo brain studies
Nathan Yoganathan and John Gillard (KalGene Pharmaceuticals Inc.), Louis Collins and Jean-Paul Soucy (McGill University), Danica Stanimirovic et Balu Chakravarthy (National Research Council Canada), Pedro Rosa-Neto (Douglas Hospital Research Centre) and Michael Waterston (Centre for Imaging Technology Commercialization (CIMTEC))	Drug Delivery across the Human Blood-Brain Barrier
Don van Meyel and Keith K. Murai (Research Institute-McGill University Health Centre), Adriana Di Polo (Research Centre of the Centre Hospitalier de l'Université de Montréal) and Timothy H. Murphy (University of British Columbia)	Cyto-iGluSnFR: A glutamate biosensor platform for brain diseases

The eye: a window to the brain

Jean-Paul Soucy (McGill University), Frederic Lesage (École Polytechnique of 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.)

$1,977,500 / 3 years

Non Invasive Identification of Aβ Plaques in Human Retina for the Diagnosis of Alzheimer's disease

Challenge: Alzheimer's disease (AD) affects millions of people worldwide, causing an irreversible and debilitating loss of neuro-cognitive functioning and the disease has no cure available at this time. Rising rates of AD are projected to take an increasing toll on individuals and their families, and to place an unprecedented burden on healthcare systems unless an effective early-stage treatment or cure is found. Currently, AD diagnosis can only be confirmed post-mortem by observing two AD hallmarks in the brain, β-amyloid (Aβ) plaques and tau strands. Diagnosing AD earlier in its course could dramatically transform the design of clinical trials to test new treatments.

Solution: A team of researchers led by Dr. Jean-Paul Soucy of McGill University will be collaborating with Optina Diagnostics in a breakthrough effort to find a cure for AD. The team is currently testing innovative technology which will detect the earliest neural hallmark of this devastating illness. Precisely, Optina Diagnostics is developing an innovative tool that will transform AD research by enabling the identification of beta-amyloid (AB) plaques, a key biomarker of the disease, before symptoms even appear. The same plaques that are found in the neurons of the brain also appear in the neurons of the retina, a light-sensitive layer lining the interior of the eye which is an extension of the brain. Optina's innovative Metabolic Hyperspectral Retinal Camera (MHRC) can detect these plaques in the retina in asymptomatic individuals by using a simple, safe and non-invasive eye test that is exceedingly more accessible than the PET scan technology currently in use.

Impact: The simple eye test could revolutionize AD research and the development of effective therapeutics. It could aid in identifying who would benefit from treatment and whether a treatment is effective. To date the development of pharmaceutical therapeutics is entirely derived from research using participants whose symptoms are already significantly progressed. This technology will enable researchers to enlist pre-symptomatic participants who are at risk for developing AD, facilitating the development of drugs targeting AD in its earliest stages, and providing the best hope for developing effective treatment and, ultimately, a cure for this devastating disease.

The DNA in the service of eye diseases
Elizabeth Simpson (University of British Columbia) and Adriana Di Polo (Research Centre of the Centre Hospitalier de l'Université de Montréal)
$1,496,062 / 3 years

Human MiniPromoters for Restricted Expression of Ocular Gene Therapy

Challenge: Blindness represents an enormous unmet disease burden in terms of human suffering and economic cost. Luckily, diseases of the eye are excellent targets for new gene-based therapies; known as gene therapy. As opposed to a drug, gene therapy is a type of biological therapy, somewhat like a vaccine. Some companies are currently conducting clinical trials for such therapies, but so far none have received approval in Canada or the United States. Because such therapies are based on genes, they need promoters, which act as switches to turn genes on and off. The team argues that, with better promoters to turn genes on and off in the right places, gene therapy will become safer and more effective. However, a major challenge is that normal human genes have very large and complex promoters, but for gene therapy the promoters need to be very small; MiniPromoters.

Solution: The team is made of five academics and one small Canadian company, and they have the proven skills necessary to make MiniPromoters. For this project, the promoters will all be made from human genes, and will be designed to act as switches with different strengths, and working in different places in the eye. The team plans to build a “toolkit” of 30 such MiniPromoters useful for different diseases of the eye, and different therapeutic approaches to loss of vision and blindness.

Impact: In this work, our “toolkit” of MiniPromoters will be pretested and made ready to be married with a wide variety of therapeutic genes developed by academic or industry researchers. Together, the team anticipates such gene therapies will have the best chance to move from clinical trials to approved treatments. This will positively impact both the companies undertaking the therapeutic development, and individuals with loss of vision or blindness due to many different rare and common diseases of the eye.

How to fool the blood-brain barrier

Rob Hutchison and Reinhard Gabathuler (biOasis Technologies Inc.), Danica Stanimirovic (National Research Council Canada), Brigitte Guérin, Roger Lecomte and David Fortin (Université de Sherbrooke)

$2,573,875 / 3 years

'Best in Class' Platform for Blood Brain Barrier Delivery of Therapeutics

Challenge: The blood-brain barrier (BBB) is a tightly woven layer of vascular cells in the brain that prevents harmful molecules from the circulation, viruses and toxins, from entering the brain. To allow entry of nutrients into the brain, the BBB employs molecular transporters that shuttle nutrients back and forth between blood and the brain across these barrier cells. Unfortunately, the same barrier that protects the brain is also an obstacle for brain delivery of therapeutics to treat brain diseases. Special strategies have to be developed to 'sneak' therapeutics passed the BBB. One such strategy is to link therapeutics to molecules that bind natural barrier transporters; potential therapeutics thus 'hitch a ride' across the barrier using a natural molecular shuttle as a Trojan horse.

Solution: In the proposed project, a Canadian company biOasis Technologies Inc, National Research Council of Canada and Université de Sherbrooke will develop very small human antibodies (10-fold smaller than regular antibodies) as molecular Trojan horses to enable delivery of therapeutics across the BBB. The team will screen thousands of antibodies to identify those that can efficiently cross the blood-brain barrier and that also can be linked to many different therapeutic molecules. The team will then develop 'fusion' molecules consisting of the BBB-crossing mini-antibody and selected therapeutics. The efficacy of these 'fusion' molecules in treating brain diseases such as brain tumors will be tested in animals. New non-invasive imaging methods by PET scan will be used to monitor brain penetration of BBB-crossing antibodies.

Impact: If proven effective, these novel BBB 'carriers' will be transferred to pharmaceutical companies who will link them to many more 'old' and new therapeutics to develop improved treatments for devastating brain disorders.

A revolutionary probe for *in vivo* studies of the brain

Janusz Pawliszyn (University of Waterloo), Dajana Vuckovic (Concordia University) and Clement Hamani (Centre for Addiction and Mental Health)

$995,427 / 3 years

Solid phase microextraction-based integrated platform for untargeted and targeted in vivo brain studies

Challenge: One of the major challenges currently faced by the pharmaceutical industry is the development of methods that can decrease the number of animals used in the drug discovery process. Comprehensive investigations of new drugs require extensive multiple determinations, and consequently, a large number of samples/animals. For that reason, alternative approaches that allow the attainment of maximum information using a minimum number of animals are urgently required. From an instrumental point of view, mass spectrometers offer increasingly sensitive and quantitative determination of biological molecules. However, collected biological samples, especially tissues, require efficient sample preparation prior to MS analysis, which is a bottleneck in a typical workflow.

Solution: This project proposes to integrate the low-invasive, non-lethal in vivo sampling/sample preparation SPME approach with MS detection to obtain the full profile of brain metabolome and lipidome, the quantification of drugs and monitoring of their metabolism, selective extraction of target compounds (drugs or selected endogenous metabolite), as well as high resolution chemical imaging of deep brain structure. This integrated analytical platform will result in fewer animals involved in the drug discovery process because no biospecimen (tissue or fluid) withdrawal is required. This in turn will reduce the overall cost of analysis, and will allow for the creation of a uniform drug discovery protocol that avoids the need for multiple sample preparation methods and the need for large animal cohorts to obtain sufficient tissue to perform all analyses needed during drug discovery process.

Impact: The proposed integrated analytical platform increases the quality of the in vivo analysis during the drug discovery process and enables to obtain more information on the effect of the stimuli on brain functioning, what allows to better understand the mechanisms behind the disease or/and its treatment. The non-lethal nature of the sampling and easy-to-operate brain sampler will significantly reduce the number of animals used, eliminate statistical inter-individual variability, and allow for the observation of long term effects of drugs in the same animals. In vivo SPME would provide breakthrough for next-generation technology in neuroscience research by bringing more effective medicines to the clinic and to the market, increasing the efficacy of existing drugs, reducing the R&D costs, time to market or the risks related to development of new drugs.

To successfully cross the blood-brain barrier
Nathan Yoganathan and John Gillard (KalGene Pharmaceuticals Inc.), Louis Collins and Jean-Paul Soucy (McGill University), Danica Stanimirovic et Balu Chakravarthy (National Research Council Canada), Pedro Rosa-Neto (Douglas Hospital Research Centre) and Michael Waterston (Centre for Imaging Technology Commercialization (CIMTEC))
$2 413 133/3 years

Drug Delivery across the Human Blood-Brain Barrier

Challenge: Of the top 10 most deadly illnesses in the world, Alzheimer's disease is the only one for which there is currently no disease-modifying therapy available. Alzheimer's disease becomes progressively more prevalent as people age, rising from over 11% of the population 65 and older to over 33% of those aged 85 and older. This devastating and deadly illness is becoming an increasingly urgent problem as the worldwide population ages.

Toxic amyloid proteins are known to be a significant contributing factor in the development of Alzheimer's disease. Abnormal clusters of protein fragments build up between nerve cells in the brain leading to impaired memory. However, delivering sufficient quantities of a safe and effective amyloid-targeting agent across the blood-brain barrier in humans has not yet been possible.

Solution: KalGene Pharmaceuticals is developing an Alzheimer's disease therapy based on a naturally-occurring agent that binds specifically to toxic amyloid-beta. When coupled with a blood-brain-barrier carrier molecule developed at the National Research Council of Canada, the compound has been successfully delivered into the brain of Alzheimer's disease models. KalGene's project with the Montreal Neurological Institute and the Centre for Imaging Technology Commercialization will proceed to demonstrate this technology in human Alzheimer's disease patients.

Impact: An effective Alzheimer's treatment would have profound personal impact for millions of people and their caregivers worldwide, as well as transform the trajectory of healthcare costs. Alzheimer's disease is one of the most feared health diagnoses. An approach to mitigating the progression of Alzheimer's disease would bring hope to patients, families and individuals at high risk. The total economic burden of dementia care in Canada alone is expected to rise from $14 billion in 2008 to $75 billion in 2028 with more than half of that attributable to Alzheimer's disease.

This project will also accelerate therapies for other brain conditions beyond Alzheimer's disease. The difficulty of delivering drugs across the blood-brain barrier has profoundly limited the development of effective therapies for diseases such as brain cancers and Parkinson's disease. By demonstrating that the blood-brain-barrier carrier technology is effective in delivering an Alzheimer's therapy in humans, will provide a valuable tool to deliver drug (s) to other neurological diseases.

Glutamate: the messenger whose flow of information is crucial in the studies of brain diseases

Don van Meyel and Keith K. Murai (Research Institute-McGill University Health Centre), Adriana Di Polo (Research Centre of the Centre Hospitalier de l'Université de Montréal) and Timothy H. Murphy (University of British Columbia)
$1,416,375 / 3 years

Cyto-iGluSnFR: A glutamate biosensor platform for brain diseases

Challenge: In the human brain and retina, the chemical glutamate is a very important messenger that carries information from one neuron to another. The levels of glutamate transmitted between neurons must be tightly controlled: too high and neurons die, too low and information is not communicated properly. In either case this can contribute to neurological diseases including stroke, glaucoma, and Alzheimer's. Glutamate levels are controlled by glial cells found next to neurons, and they do this my taking up glutamate through one of two types of transporter proteins on their surface called EAATs. The EAATs are very attractive targets for the development of new drug therapies. However, compounds that modify EAAT function have been difficult to identify due to a lack of available tools.

Solution: Cyto-iGluSnFR (pronounced "sight-oh-eye-glue-sniffer") is a new breakthrough technology that the team intends to adapt for the discovery of EAAT-based drugs to treat a variety of brain and eye diseases. Cyto-iGluSnFR is an engineered protein that senses glutamate, allowing scientists to see and measure the rate by which glutamate enters cells. With this funding the team plans to adapt this Cyto-iGluSnFR glutamate biosensor in order 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. These potential drugs can then be further tested using the very same biosensor in laboratory mice - where neurons and glial cells function as they do in humans - in order to make sure they are safe and effective for patients.

Impact: The Cyto-iGluSnFR platform is likely to have impact at each of the following main steps in the drug discovery process: Target identification, Discovery/Screening, Lead optimization, and Preclinical Testing. By adapting Cyto-iGluSnFR for multiple stages of drug development and testing, our team of experts will build a comprehensive platform to accelerate progress toward new therapies for brain and eye diseases.