2024 IRIC NEXT GENERATION COMPETITION

INTERNSHIP PROJECTS

INSTITUTE FOR RESEARCH
IN IMMUNOLOGY
AND CANCER

IRIC

Université de Montréal

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INTERNSHIP PROJECTS

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Internship project #1

Understanding immunogenic nuclear reassembly defects after cell division

Under the supervision of Vincent Archambault
Cell Cycle Regulation Research Unit

PROJECT DESCRIPTION

Mitosis is the partition of the cellular nucleus that occurs during cell division. For this process, the nuclear envelope is broken, allowing condensed chromosomes to be segregated on a spindle apparatus. At the end of mitosis, a nucleus must be reassembled in each of the two newborn cells as they enter interphase. Research in our lab aims to understand the complex molecular mechanisms regulating this process. Cancer cells divide chaotically and often develop visible defects in the structure of their nuclei. Recent research has identified an intracellular response enabling cells with nuclear defects to call for their destruction by lymphocytes. The project proposed aims to better understand how post-mitotic nuclear defects trigger this response, and to identify the precise mitotic mechanisms whose perturbations can maximize this response. Ultimately, we envision that inducing nuclear reassembly defects in cancer cells pharmacologically could stimulate the elimination of these cells by the immune system. For this project, the selected student will join a collaborative and multidisciplinary effort. They will receive close supervision at first, and will gradually develop competence and autonomy with multiple techniques through the summer.

See the lab's external website (with movies): http://www.archambault.iric.ca

LAB TECHNIQUES

Human cell cultue
Microscopy
Molecular Biology
Biochemistry
Genetics

FOR MORE INFORMATION

iric.ca/en/research/principal-investigators/vincent-archambault
archambault.iric.ca

Internship project #2

Characterization of bio/chemical interactions at the surface of nanocarbon-FET biosensors

Under the supervision of Delphine Bouilly
Design and Application of Electronic Nanobiosensors Research Unit

PROJECT DESCRIPTION

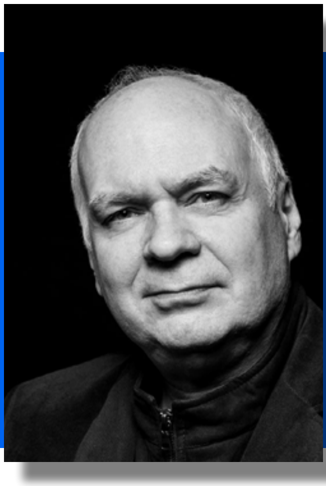
In our laboratory, we work on the development of electronic biosensors for the detection of proteins and nucleic acids. These sensors are made of field-effect transistor (FET) devices based on functionalized conductive nanocarbon materials, such as atomically-thin graphene or carbon nanotubes. Nanocarbon-FETs are a promising technology for the quantitative detection of biomarkers, offering unique advantages such as simplicity, low-cost fabrication and label-free real-time electrical readout. The goal of this project is to characterize surface interactions between biological molecules and graphene devices, using electrical measurements of the nanosensors and high-resolution surface microscopy. These experiments will be used to optimize sensitivity metrics of these sensors for the detection of cancer biomarkers.

LAB TECHNIQUES

Microfabrication & micro/nanoelectronics
Surface chemistry
Bioconjugation chemistry
High-resolution microscopy

FOR MORE INFORMATION

https://www.iric.ca/en/research/principal-investigators/delphine-bouilly



Internship project #3

Evolutionary-based reengineering of G protein-coupled receptors signaling selectivity

Under the supervision of Michel Bouvier
Molecular Pharmacology Research Unit

PROJECT DESCRIPTION

With more than 800 members in humans, the G protein-coupled receptors (GPCRs) familly represents the largest class of proteins involve in cell signalling and, as such, these receptors represent the targets for more than 30% of prescription drugs. They transduce the signal of hormones, neurotransmitters, chemokines and drugs by engaging intracellular signaling partners including hetero-trimeric G proteins. The G proteins are divided in 4 families based on the nature of their alpha subunit, Gs, Gi/o/z, G12/13, Gq/11. Until recently, GPCR were believe to be highly selective and to activate only one family of G proteins. More recently it has been shown that whereas some GPCR show exquisite selectivity for a G protein family or even among family members, others are promiscuously activating members of 2,3 or even the 4 families of G proteins. This has important physiological and potentially therapeutic consequences as the functional selectivity of the receptors may determine their therapeutic efficacy and safety profile. Yet, the molecular determinant of GPCR-G protein selectivity remains poorly understood. Based on the phylogenetic comparisons of hundreds of GPCR and of their G protein selectivity, specific receptor sequences can be predicted to dictate the ability of the receptor to activate different subsets of G proteins. In the present project the trainee will test these prediction by substituting the proposed selectivity-directing sequences in the native sequence of selected GPCRs and testing the impact of these site-directed mutations on the coupling selectivity of the receptor using bioluminescence resonance energy transfer-based biosensors to measure the activation of the downstream G proteins.

LAB TECHNIQUES

Cell culture
Heterologous protein expression
Site-directed mutagenesis
Western Blot ELISA
Bioluminescence Resonance Energy Transfer (BRET)
Phylogenetic analysis

FOR MORE INFORMATION

https://www.iric.ca/en/research/principal-investigators/michel-bouvier

Internship project #4

Study of mechanisms regulating metabolic changes in treatment-resistant breast cancers

Under the supervision of Geneviève Deblois
Metabolic and Epigenetic Alterations in Cancer Research Unit

PROJECT DESCRIPTION

A common feature of aggressive cancers is their ability to tolerate antitumor treatments exposure such as chemotherapy. The development of chemotherapy resistance comes with metabolic changes in the cancer cells. In addition of meeting the energetic, anabolic and antioxidants needs of cancer cells, these metabolic alterations can also affect the cancer cells identity by altering their epigenomes, since chromatin-modifying enzymes are regulated by the abundance of certain metabolites. Therefore, it is essential to understand how cancer cells adapt their metabolism when developing resistance to therapies in order to improve the effectiveness of antitumor treatments. We have identified metabolic changes that promote the survival of breast cancer cells when exposed to certain chemotherapies. Our work suggests that these metabolic adaptations affect some epigenetic modifications of chemoresistant breast cancer cells. The aim of this internship is to better understand the mechanisms that regulate this metabolism reprogramming as well as their consequences on the epigenetic profiles of chemoresistant breast cancer cells. This project will identify new vulnerabilities that could be exploited to better target breast cancers that are resistant to chemotherapy.

LAB TECHNIQUES

Molecular Biology
Cell Culture
Chromatin immunoprecipitation
qPCR
Metabolic profiling

FOR MORE INFORMATION

iric.ca/en/research/principal-investigators/genevieve-deblois

Internship project #5

Novel Chimeric Antigen Receptor designs for the treatment of solid tumors

Under the supervision of Étienne Gagnon
Cancer Immunology Research Unit

PROJECT DESCRIPTION

Our lab has created a novel Chimeric Antigen Receptor (CAR) scaffold which displays natural surface expression, low-to-no tonic signaling, and is highly efficient in treating ‘liquid’ tumors such as B cell leukemia (B-ALL). This new receptor design is highly optimizable and lends itself nicely to other cell types such as macrophages, dendritic cells and NK cells. The goal of the project is to design, produce and validate receptors that go beyond CAR-T applications, which may be more conducive to the treatment of solid tumors. The end goal of this project is to introduce hematopoietic stem cell-derived CAR expressing cellular armadas for the treatment of solid tumors such as colorectal cancer, melanoma and breast cancer.

LAB TECHNIQUES

Molecular Biology
Lentivirus production
Cell culture: cell lines
Cell culture: primary cells
Flow cytometry

FOR MORE INFORMATION

https://www.iric.ca/en/research/principal-investigators/etienne-gagnon

Internship project #6

Role of SCL interacting partners for hematopoiesis and leukemia development

Under the supervision of Trang Hoang
Hematopoiesis and Leukemia Research Unit

PROJECT DESCRIPTION

Our laboratory is interested in the molecular mechanisms responsible for the development of hematopoiesis and the formation of acute leukemia. We have identified novel interacting partners of the SCL complex, a multifactorial transcriptional complex acting at multiple levels in the hematopoietic system. The first objective of the project is to confirm in vitro the interaction of the SCL complex members and the newly identified partners by different molecular approaches. In addition, the functional consequences of these interactions will be studied in an ex vivo system reproducing the hematopoietic niche and allowing the differentiation of normal and leukemic primary stem cells.

LAB TECHNIQUES

Molecular Biology (qPCR, cloning)
Immunoprecipitation
Western blot
Cell culture (cell lines and primary cells)
Flow cytometry
Genetics (mouse model)

FOR MORE INFORMATION

iric.ca/en/research/principal-investigators/trang-hoang

Internship project #7

Defining the molecular mechanisms leading to the development of acute leukemia

Under the supervision of Trang Hoang
Hematopoiesis and Leukemia Research Unit

PROJECT DESCRIPTION

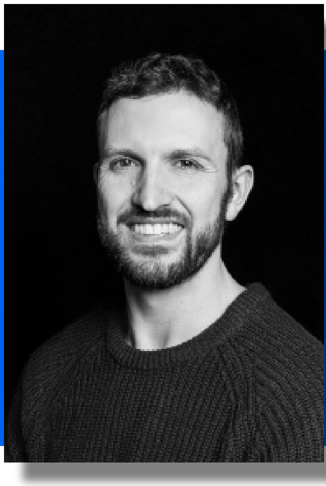
We have identified the thymocyte subpopulation that is at the origin of acute leukemia induced by the SCL and LMO1 oncogenes. To generate leukemia, these pre-leukemic stem cells (pre-LSCs) must escape several intrinsic molecular controls acting in the cell. The research project aims in understanding how pre-LSCs manage to bypass these surveillance mechanisms and adapt to oncogenic stress. A better understanding of these mechanisms will lead to the identification of therapeutic vulnerabilities and drugs for specific treatment of leukemia patients.

LAB TECHNIQUES

Molecular Biology (qPCR)
Cell biology (culture of primary cells)
Flow cytometry
Genetics (mouse model)
Bioinformatics analysis (RNAseq)

FOR MORE INFORMATION

iric.ca/en/research/principal-investigators/trang-hoang



Internship project #8

Cellular models for cancer and regenerative medicine

Under the supervision of David Knapp
Cellular Engineering Research Unit

PROJECT DESCRIPTION

Several projects are available depending on candidate interests. These include modeling concussion and therapies to treat it using human cerebral organoids, modeling leukemia development with the genome engineering of primary human hematopoietic stem cells, and computational modeling of cell differentiation and treatment response in pancreatic tumours. Students (on wet lab projects) will perform live-cell imaging, immunofluorescence, flow cytometry, CRISPR/Cas9 mediated precise genome editing, molecular cloning, stem cell culture. Students interested in computational projects will work with single-cell RNA and ATAC-seq data, classical and AI based gene regulatory network models and agent-based modeling. They will work under the day-to-day direction of a senior PhD student who is directing the project. There will also be opportunities to learn other techniques and contribute to other projects.

LAB TECHNIQUES

Cell culture
Magnetic cell separation
Nucleofection
Precise genome editing by CRISPR
Live-cell imaging
Flow cytometry
PCR
Gel electrophoresis

FOR MORE INFORMATION

iric.ca/en/research/principal-investigators/david-knapp

Internship project #9

Understanding how adult stem cells divide in vivo

Under the supervision of Jean-Claude Labbé
Cell Division and Differenciation Research Unit

PROJECT DESCRIPTION

How do adult stem cells divide *in vivo*, in response to niche signaling? Answering this question has been challenging, mainly due to the lack of appropriate models to visualize stem cells *in vivo*. We have developed a novel method to image the division of adult stem cells in vivo, using the nematode *Caenorhabditis elegans* (*C. elegans*) as model organism. Genetic analysis has revealed specific pathways and regulators that are essential to coordinate stem cell division during development and aging of the animal. We are seeking motivated individuals to pursue the characterization of some of these regulators, to better understand how they contribute to the regulation of stem cell division, using genetic analysis and high-resolution time-lapse imaging approaches.

LAB TECHNIQUES

RNAi
Genetic analysis
In vivo time-lapse imaging
Quantitative image analysis
Caenorhabditis elegans

FOR MORE INFORMATION

iric.ca/en/research/principal-investigators/jean-claude-labbe

Internship project #10

Enhancing Drug Discovery with Deep Learning and Gene Expression Profiling

Under the supervision of Sébastien Lemieux
Functional and Structural Bioinformatics Research Unit

PROJECT DESCRIPTION

Machine learning approaches have been promising for a long time the ability to predict small molecule activities to accelerate hit identification in drug discovery. Recent advances in deep learning (such as Graph Convolutional Neural Networks, GCNN) are renewing this hope, but so far with relatively limited success in practice. We suspect that the main challenge that these algorithms encounter is the cryptic and incomplete numerical representation used to input small molecules into neural networks. Here, we aim to replace the traditional molecular graph representations (such as molecular fingerprints or GCNN) with expression profiles derived from live human cells exposed to each compound. Through the development of programs in the Julia language, the trainee will work on publicly available datasets which consist of gene expression profiles for thousands of small molecules applied to over a hundred of cell lines. The project aims to develop a neural network approach to characterize the trios small molecules, genes, and cell lines. For this purpose, a specialized neural network architecture will be tailored to handle this three-part input representation. The network will be equipped with attention mechanisms and specialized layers to effectively process gene expression profiles. Additionally, techniques such as transfer learning and ensemble methods may be explored to enhance the model's predictive capabilities. Ultimately, this transformative approach has the potential to revolutionize the field of drug discovery by providing a more accurate and biologically meaningful prediction of small molecule activities. By leveraging the power of deep learning and incorporating live human cell expression profiles, we aim to significantly accelerate the hit identification process, leading to the development of more effective drugs for a wide range of diseases.

LAB TECHNIQUES

Programing in Julia
Data analysis
Neural Network Development
Model Validation
Chemoinformatic

FOR MORE INFORMATION

iric.ca/en/research/principal-investigators/sebastien-lemieux

Internship project #11

Mechanisms of action of full antiestrogens in breast tumor cells

Under the supervision of Sylvie Mader
Molecular Targeting for Breast Cancer Treatment Research Unit

PROJECT DESCRIPTION

About 2/3 of breast tumors express or overexpress the estrogen receptor and its growth is stimulated by estrogen. Anti-estrogens are competitive inhibitors of estrogen receptors. There are two classes of antiestrogens, which act by different mechanisms. The goal of this project is to characterize the mechanisms of action of anti-estrogen such as fulvestrant, a drug used as a second-line therapy for tumors that are resistant to tamoxifen. Our results indicate that anti-estrogens induce SUMOylation of the receptor and its interaction with a chromatin remodeling complex. The goal of the project is to characterize the importance of these effects in the anti-estrogenicity of fulvestrant.

LAB TECHNIQUES

Cell culture
Western blot
Chromatin immunoprecipitation
Luciferase assay

FOR MORE INFORMATION

iric.ca/en/research/principal-investigators/sylvie-mader

Internship project #12

Molecular basis of breast cancer heterogeneity

Under the supervision of Sylvie Mader
Molecular Targeting for Breast Cancer Treatment Research Unit

PROJECT DESCRIPTION

Breast cancer is a heterogeneous disease, breast tumors being classified into different subtypes based on expression of specific molecular markers such as estrogen receptor alpha. Our laboratory has identified a group of transcription factors whose differential expression can identify the main breast cancer subtypes. Our current goal is to assess how these transcription factors determine the phenotype of each subtype and to identify therapeutic targets, especially for subtypes that do not currently benefit from targeted therapies.

LAB TECHNIQUES

Cell culture
Western blot
RT-qPCR
shRNA/siRNAs
CRISPR-Cas9

FOR MORE INFORMATION

iric.ca/en/research/principal-investigators/sylvie-mader

Internship project #13

Optimization of compounds as potential therapeutic agents

Under the supervision of Anne Marininer
Drug Discovery Research Unit

PROJECT DESCRIPTION

The internship position will be with the Medicinal Chemistry Platform of the Institute for Research in Immunology and Cancer (IRIC) at the Université de Montréal (UdeM). During his/her term, the intern will be working with a team of experienced chemists, under the direct supervision of a Ph.D. and/or M.Sc.-level scientist.

The Medicinal Chemistry Platform has a long-standing research partnership with a major pharmaceutical company and is currently engaged in the hit and lead optimization phases of full drug discovery programs. As part of this effort, the student will have full access to program-related data and proprietary structures. The expectation is that the student will be doing hands-on synthesis at the bench, in order to generate designated target molecules to be submitted for biological evaluation. This will involve all aspects of synthetic organic chemistry, including preparation, isolation, purification and spectral analysis of small molecules in various lead series. The work will also necessitate conscientious record-keeping, in the form of a research notebook, and the effective oral and written communication of research results. In order to further develop an understanding of medicinal chemistry, the student will be encouraged to participate in the critical analysis of structure-activity relationships generated by themselves and others and in devising potential strategies for addressing relevant program issues.

The student will be expected to work effectively within a diverse and multi-site team of collaborators, including chemists, molecular biologists, pharmacologists, toxicologists, CADD specialists, etc. As such, the intern will be exposed to all aspects of the drug discovery process and will have a genuine opportunity to make significant contributions to a promising drug discovery program, all in the context of a unique university-industry alliance.

LAB TECHNIQUES

Synthetic organic chemistry:
Preparation, isolation, purification and spectral analysis.

FOR MORE INFORMATION

iric.ca/en/research/principal-investigators/anne-marinier

Internship project #14

Functional implication of selected genetic events in hematopoietic stem cells self-renewal and leukemic transformation

Under the supervision of Guy Sauvageau
Molecular Genetics of Stem Cells Research Unit

PROJECT DESCRIPTION

Next-generation sequencing has greatly refined the genetic and transcriptional landscapes of hematopoietic cells. Newly uncovered mutations and pathways are now thought to play key roles in governing the fate of the hematopoietic system, but until now have not been confirmed experimentally. We now envision to functionally test the implication of some of these genetic events in the self-renewal of hematopoietic stem cells as well as in the induction of acute leukemia transformation.

The selected student will actively participate in every stages of the project, from the molecular sub-cloning of candidate genes, the production of transducing viral particles, the handling of primary human samples to the final analysis of hematopoietic cell biology using well-established cell-based assays.

Along the way, recent genetic engineering technologies such as shRNA and CRISPR shall be implemented to knock-down additional transcripts of interest in various cell systems (cord blood cells, AML cell lines, primary AML cells) to assess their molecular functions in acute myeloid leukemia progression and stem cell biology.

LAB TECHNIQUES

Cell culture
Flow cytometry
Cloning
qPCR

FOR MORE INFORMATION

iric.ca/en/research/principal-investigators/guy-sauvageau

Internship project #15

Rewiring of cancer-initiating signals to cell death and senescence pathways as a therapeutic strategy

Under the supervision of Matthew J. Smith
Cancer Signaling and Structural Biology Research Unit

PROJECT DESCRIPTION

The RAS GTPases are fundamental regulators of normal development, causative agents in an extraordinary number of human cancers, and key determinants in several developmental disorders termed RASopathies. RAS proteins are encoded by three proto-oncogenes: HRAS, KRAS and NRAS. Of these, KRAS mutations are most frequent in human cancers, present in 22% of all tumours and 61% of pancreatic, 33% of colon and 17% of lung cancers. These are amongst the most clinically refractory cancers we have today, representing the first, third and fourth leading causes of cancer death worldwide. Despite extensive effort over three decades, there remain no clinically successful drugs that target RAS itself. We thus require new approaches to target these cancer-causing proteins, and current approaches are focus on downstream 'effector' pathways through which RAS transmits its activating signals. Several current therapies target activating pathways via inhibition, but the antithesis of such an approach, rewiring or stimulating pathways that control cell death (apoptosis), should also have efficacy. This internship project will contribute to our work in understanding how RAS interacts with proteins involved in apoptosis and control of cellular senescence. The final objective will be creation of RAS mutants that 'rewire' signaling to effective self-termination, with eventual look to small molecule screens for identification of compounds targeting the characterized mutation sites. To accomplish these aims we need to first characterize how individual RAS and RAS-binding proteins interact in a biochemical and structural sense. The trainee will be involved in cloning, expression and production of these proteins. Upon successful isolation of purified components, we will undergo screens to identify crystallography conditions for eventual structure determination of the RAS-effector complexes. This project will improve our knowledge of RAS biochemistry and biology, with an end goal to better the treatment, diagnosis, and prevention of RAS-driven cancers.

LAB TECHNIQUES

Cloning
Protein Biochemistry
X-Ray Crystallography
Tissue Culture

FOR MORE INFORMATION

iric.ca/en/research/principal-investigators/matthew-smith

Internship project #16

Defining the molecular mechanism of action of novel compounds on acute myeloid leukemia cells

Under the supervision of Brian Wilhelm
High-Throughput Genomics Research Unit

PROJECT DESCRIPTION

The intern will work with lab members (grad students/research assistant) to characterize the molecular mechanism by which specific drugs block the growth of leukemia cells. Acute myeloid leukemia develops when normal blood stem cells acquire mutations that prevent them from either dying or differentiating. As a result, the progenitor cells continue to grow in the bone marrow blocking normal hematopoiesis. We have recently performed a small molecules screen using 12,000 compounds against 20 patient and model AML samples and have identified a small number of compounds that block AML growth but do not affect normal blood stem cells. We are now looking at these compounds individually to try and understand what they target in the cell and how this prevents the AML cells from growing. This work typically involves treating cells with individual drugs, monitoring specific protein levels or activities or gene expression levels. Because each compound may be acting differently, and on different cellular targets, a range of different approaches must generally be used to elucidate the nature of the anti-AML activity of the drugs.

LAB TECHNIQUES

Cell culture
PCR
Western blotting
NGS analysis
qRT-PCR
Standard molecular cloning

FOR MORE INFORMATION

iric.ca/en/research/principal-investigators/brian-wilhelm