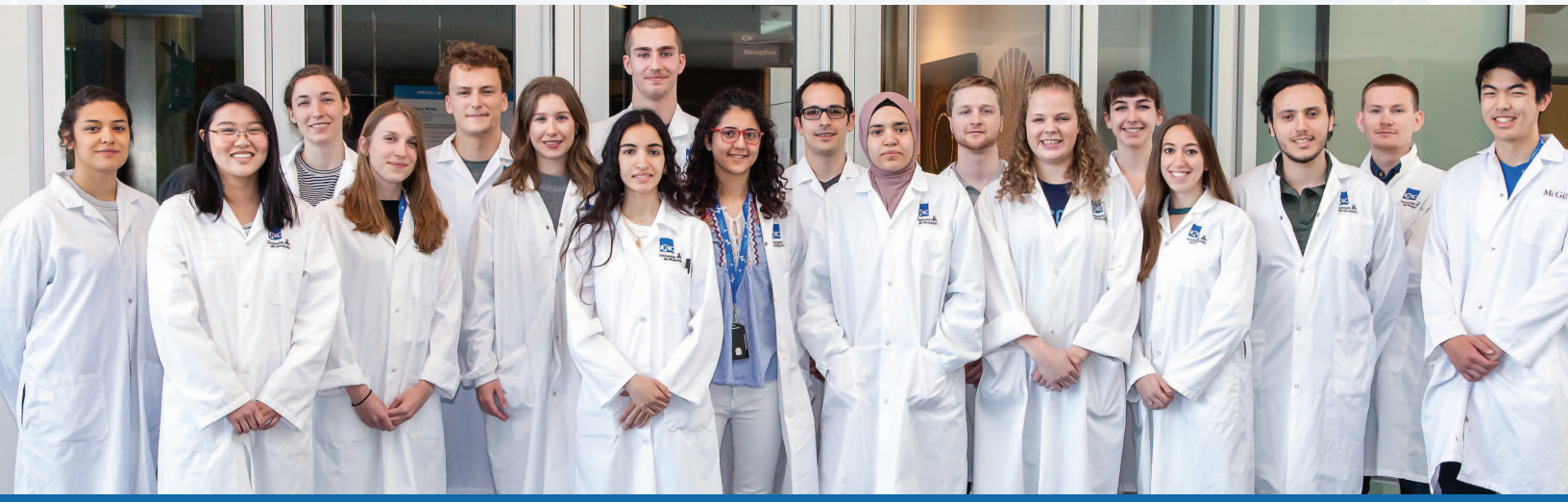


2019 IRIC NEXT GENERATION AWARDS

INTERNSHIP PROJECTS

INSTITUTE FOR RESEARCH
IN IMMUNOLOGY
AND CANCER

IRIC

Université de Montréal

2019 IRIC NEXT GENERATION AWARDS

INTERNSHIP PROJECTS

Project #1	The molecular mechanisms of cell division Under the supervision of Vincent Archambault	p. 3
Project #2	Structural and molecular determinants of the functional selectivity of G protein-coupled receptors Under the supervision of Michel Bouvier	p. 4
Project #3	Study of the epithelial mesenchymal transformation in metastatic cells Under the supervision of Sébastien Carréno	p. 5
Project #4	Ral as a new regulator of collective cell migration Under the supervision of Gregory Emery	p. 6
Project #5	Role of anionic lipids within the inner leaflet of the plasma membrane in immune receptors regulation Under the supervision of Étienne Gagnon	p. 7
Project #6	Understanding the age-associated increase in cell differentiation stability associated with short telomeres Under the supervision of Lea Harrington	p. 8
Project #7	Mechanisms controlling leukemic stem cell self-renewal: genetic and pharmacologic approaches Under the supervision of Trang Hoang	p. 9
Project #8	Characterization of the mitotic motor protein kif14 that is linked to cancer progression Under the supervision of Benjamin Kwok	p. 10
Project #9	Evaluation of chemical inhibitors of motor proteins *in vitro* and in live cells Under the supervision of Benjamin Kwok	p. 11
Project #10	Understanding how adult stem cells divide *in vivo* Under the supervision of Jean-Claude Labbé	p. 12
Project #11	Exploratory Analyses of Machine Learning Approaches for Transcriptomics Data Normalization Under the supervision of Sébastien Lemieux	p. 13
Project #12	Deep learning algorithms for precision medicine Under the supervision of Sébastien Lemieux	p. 14
Project #13	Mechanisms of action of full antiestrogens in breast tumor cells Under the supervision of Sylvie Mader	p. 15
Project #14	Bioinformatics of personalized targeted therapies against cancer Under the supervision of François Major	p. 16
Project #15	Calibrating protein output Under the supervision of François Major	p. 17
Project #16	Optimization of compounds as potential therapeutic agents Under the supervision of Anne Marinier	p. 18
Project #17	Role of the atypical MAP kinase ERK3 in cancer progression Under the supervision of Sylvain Meloche	p. 19
Project #18	Characterization of novel effectors of the Ras/MAPK pathway in cancer Under the supervision of Philippe P. Roux	p. 20
Project #19	Functional implication of selected genetic events in hematopoietic stem cells self-renewal and leukemic transformation Under the supervision of Guy Sauvageau	p. 21
Project #20	Rewiring of cancer-initiating signals to cell death and senescence pathways as a therapeutic strategy Under the supervision of Matthew J. Smith	p. 22
Project #21	Characterization of new Ras/MAPK pathway components Under the supervision of Marc Therrien	p. 23
Project #22	Dynamic immunopeptidome and its significance in leukemia immunotherapy Under the supervision of Pierre Thibault	p. 24
Project #23	A novel strategy for discovery of sirtuin inhibitors Under the supervision of Alain Verreault	p. 25
Project #24	Functional and chemogenomic studies of pediatric acute myeloid leukemia Under the supervision of Brian Wilhelm	p. 26

Internship project #1

The molecular mechanisms of cell division

Under the supervision of Vincent Archambault
Cell Cycle Regulation Research Unit

PROJECT DESCRIPTION

Cancer is defined by excessive cellular proliferation. Our laboratory is interested in understanding the molecular mechanisms that control cell division. In mitosis, chromosomes condense and separate on a spindle of microtubules before cytokinesis. The genes and proteins involved are strongly conserved between species and are mutated in cancers. We use cells in culture and the fly Drosophila as models. Our fundamental discoveries improve our molecular understanding of the process of cell division and of its regulation. This knowledge serves as a basis for the design of new targeted anti-cancer therapies that block cell division. The specific subject of the project will depend on what is most exciting in the lab at that time, and the choice will be made also following the student's preferences.

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

LAB TECHNIQUES

Microscopy
Imaging
Molecular Biology
Biochemistry
Genetics

FOR MORE INFORMATION

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

Internship project #2

Structural and molecular determinants of the functional selectivity of G protein-coupled receptors

Under the supervision of Michel Bouvier
Molecular Pharmacology Research Unit

PROJECT DESCRIPTION

Based on the 3D crystal structure of the β2-adrenergic receptor, the Bouvier laboratory has identified receptor domains and residues that play specific roles in activating distinct downstream effectors (*e.g.* Gs, Gi, β-arrestins, cAMP production, MAPK activation, endocytosis, etc). This allows proposing a molecular/structural basis explaining ligand-biased signalling (*i.e.* different ligands can modulate distinct downstream effectors with different efficacies) of G protein-coupled receptors. The project will aim at assessing the influence of the diverse receptor domains and residues in the functionally selective response of a collection of β-adrenergic ligands. The response profiles obtained for different ligands will then be translated in structural terms to determine the receptor conformational states responsible for ligand-biased functional selectivity. This project should provide new pharmacological and structural knowledge that could be used to rationally design new classes of drugs with define signalling selectivity and thus, improved therapeutic potential.

LAB TECHNIQUES

Site-directed mutagenesis
Cell culture
Protein heterologous expression
Western blot analysis
ELISA
Receptor activity and second messenger generation using BRET-based biosensors

FOR MORE INFORMATION

iric.ca/en/research/principal-investigators/michel-bouvier

Internship project #3

Study of the epithelial mesenchymal transformation in metastatic cells

Under the supervision of Sébastien Carréno

Cellular Mechanisms of Morphogenesis during Mitosis and Cell Motility Research Unit

PROJECT DESCRIPTION

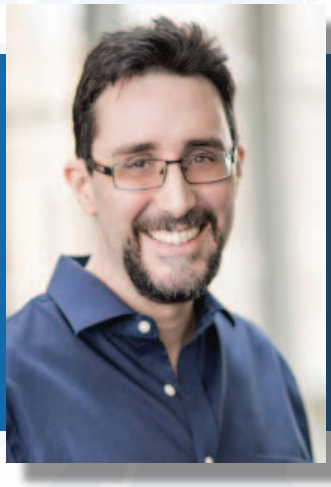
90% of cancer patients die from abnormal migration of cancer cells (metastasis) throughout the body. The epithelial-mesenchymal transition (EMT) allows cells to acquire the ability to migrate through the body. This process is normally restricted to the development of the embryo and is therefore turned off after birth. However, cancer cells are able to reprogram the TEM to migrate and to form metastases. Understanding how cancer cells reprogram the TEM is therefore an important challenge for fundamental and biomedical research. Our laboratory has discovered a mechanism that blocks the TEM in healthy cells (JCB 2008 JCB 2011 JCB 2013). Our work suggests that cancer cells bypass this mechanism to reprogram the TEM and metastasize. This project aims to better understand the basic mechanism that we have identified and thus better understand how cancer cells are reprogramed. It is of crucial importance since it will allow to define targeted anti-metastatic strategies to fight against cancer.

LAB TECHNIQUES

Molecular biology
Cell biology
Biochemistry
5D time-lapse microscopy

FOR MORE INFORMATION

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



Internship project #4

Ral as a new regulator of collective cell migration

Under the supervision of Gregory Emery
Vesicular Trafficking and Cell Signalling Research Unit

PROJECT DESCRIPTION

Collective cell migration is involved in many developmental events, but also in pathologies and in the dissemination of cancer cells. By using the Drosophila model system, we have identified new regulators of collective cell migration regulating cell coordination. The student will further analyse the function of a kinase involved in this process by using cutting edge microscopy techniques.

LAB TECHNIQUES

Drosophila genetics
Confocal microscopy
General cell biology techniques

FOR MORE INFORMATION

iric.ca/en/research/principal-investigators/gregory-emery
emery.iric.ca

Internship project #5

Role of anionic lipids within the inner leaflet of the plasma membrane in immune receptors regulation

Under the supervision of Étienne Gagnon
Cancer Immunobiology Research Unit

PROJECT DESCRIPTION

This project aims to determine the role of anionic lipids, such as phosphatidylserine, in regulating the activation of immune receptors such as CD2 in T cells. We have already shown that the TCR components CD3 chains are dynamically bound to the inner leaflet through electrostatic interactions between the positively charged amino acids with the cytoplasmic domains of the TCR-CD3 chains and the negatively charged phosphatidylserine of the PM. This, we showed, was directly linked to the innate control of the phosphorylation of the TCR. We have now identified a new immune receptor, CD2, also expressed at the surface of T cells which shows the same electrostatic signature in amino acid composition as the TCR-CD3 cytoplasmic chains; however nothing is known about how this receptor's phosphorylation and function is regulated by such interaction. The proposed project aims to study the binding capacity of the CD2 cytoplasmic chains with the PM to determine if a similar mechanism in receptor activation control is in place when compared to TCR-CD3. These results would form the basis of an article, but also additional long-term funding for the lab. Finally gaining insights into how phospholipids, such as phosphatidylserine, modulate immune receptor sensitivity may enable us to design novel therapies to treat immune defects such as cancer and autoimmunity.

LAB TECHNIQUES

Protein production and purification
In vitro and *in vivo* FRET assay
Flow cytometry
Cell culture,
Molecular biology

FOR MORE INFORMATION

iric.ca/en/research/principal-investigators/etienne-gagnon

Internship project #6

Understanding the age-associated increase in cell differentiation stability associated with short telomeres

Under the supervision of Lea Harrington

Telomere Length Homeostasis and Genomic Instability Research Unit

PROJECT DESCRIPTION

To assess whether human cells of different ages (in culture, or isolated from different aged individuals) possess a different ability to respond to differentiation inducing cues by virtue of their telomere status. Human cells will be grown in culture and stimulated to differentiate using different agents. The effect of cell age, donor age, and telomere integrity will be compared, with the goal of answering the question whether the telomere instability associated with older aged cells leads to a defect in cell differentiation stability.

LAB TECHNIQUES

Human cells culture
Flow cytometry
Western blot
qPCR, qPCR array
Chromatin immunoprecipitation
Differentiation assay with human cells
Immunofluorescence (qFISH)
Telomere Restriction Fragment (TRF blot)
Molecular Biology (enzymatic assay for telomerase, ...)

FOR MORE INFORMATION

iric.ca/en/research/principal-investigators/lea-harrington

Internship project #7

Mechanisms controlling leukemic stem cell self-renewal: genetic and pharmacologic approaches

Under the supervision of Trang Hoang
Hematopoiesis and Leukemia Research Unit

PROJECT DESCRIPTION

Acute leukemias are maintained by a rare subpopulation of leukemic stem cells that can escape chemotherapy.

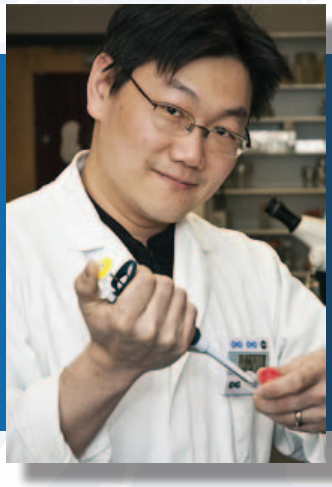
We have identified novel small molecule inhibitors of leukemic stem cells. The project consists in defining the mechanisms through which these compounds reveal the vulnerabilities of leukemic stem cells.

LAB TECHNIQUES

Transgenic mouse models of acute leukemia
Flow cytometry
Cell purification
RT-PCR
Cell culture
Transplantation assays
Analyses of dose-response curves

FOR MORE INFORMATION

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



Internship project #8

Characterization of the mitotic motor protein kif14 that is linked to cancer progression

Under the supervision of Benjamin Kwok
Chemical Biology of Cell Division Research Unit

PROJECT DESCRIPTION

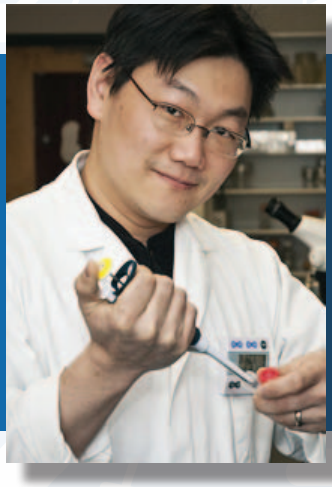
The mitotic kinesin kif14 has been shown to be overexpressed in multiple cancers. Its overexpression correlates positively with disease progression and poor prognosis. In addition, kif14 is a prime candidate oncogene on chromosome 1q32, a hot spot of genomic gain found in many of these cancers. Depletion of kif14 in cultured human cancer cells lead to chromosome segregation defects, cytokinesis failure, and apoptosis. Despite its importance, kif14 is one of the most understudied kinesins. There are less than 40 articles on kif14 published to date. The molecular basis of kif14's role in tumorigenesis and in mitosis remains largely unknown. We have successfully purified active recombinant kif14 constructs and solved the crystal structure of Kif14 motor domain (Arora et al., J Mol Biol. 2014). Our data revealed many properties of Kif14 that are distinctly different from conventional microtubule-based motors. The goal of the internship project is to understand how these characteristics link to kif14 functions and to validate our findings in living cells. Results obtained from this study will be crucial to understand kif14's role in cell division and tumorigenesis.

LAB TECHNIQUES

Molecular biology
Protein biochemistry
High-resolution microscopy
Cell culture

FOR MORE INFORMATION

iric.ca/en/research/principal-investigators/benjamin-kwok



Internship project #9

Evaluation of chemical inhibitors of motor proteins *in vitro* and in live cells

Under the supervision of Benjamin Kwok
Chemical Biology of Cell Division Research Unit

PROJECT DESCRIPTION

The formation of the mitotic spindle, a microtubule-based machine, is required for chromosome segregation during cell division. Inhibition of spindle assembly blocks cell division and is a viable mean to treat cancer. Paclitaxel, one of the most successful chemotherapeutics, targets tubulin, which is the building block of microtubules, and inhibits its polymerization dynamics. However, its success has been limited by the development of drug resistance in patients. Therefore, alternative strategies are needed to overcome this hurdle. Kinesin motor proteins which have the ability to control microtubule organization and polymerization dynamics provide attractive targets for chemical inhibition. Recently, we have completed two high-throughput screens to identify small molecule chemical inhibitors for kinesins. From 110,000 compounds that we have screened, we obtained about more than one hundred candidate hits with different level of selectivity against different kinesin families. We have now completed the initial phase of characterizing the candidate hit compounds in vitro using biochemical assays and in cells using high-resolution microscopy. In fact, we have published the characterization of one of these compounds recently (Talje et al., FEBS Lett. 2014). This internship project is to help determine the precise mechanisms of action of these kinesin inhibitors on enzymatic activity of the motor proteins and their impact on mitotic processes such as spindle assembly and chromosome segregation. Our ultimate goal is to understand how we can use these small molecules to suppress cell proliferation as a way to treat cancer.

LAB TECHNIQUES

Biochemistry
Cell culture
Microscopy

FOR MORE INFO

iric.ca/en/research/principal-investigators/benjamin-kwok

Internship project #10

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 #11

Exploratory Analyses of Machine Learning Approaches for Transcriptomics Data Normalization

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

PROJECT DESCRIPTION

The goal of this summer stage is to explore the transcriptomics normalization techniques in order to detect and remove potential batch effects the datasets may contain.

High-throughput sequencing data acquisition allows a wide spectrum of transcriptomics analyses, ranging from functional annotations of genes to even refined molecular diagnostics. However, many challenges remain when addressing the problem of harmonizing datasets from different origins. The causes of these non-biological biases may come from numerous sources; eg. handlers, reagents, processing day or time, etc. If they are not dealt with properly, batch effects might be confounded with the true biological response and lead to erroneous experimental conclusions.

Therefore, we aim to use and benchmark normalisation algorithms that attempt to suppress batch effects. These protocols, drawn from the literature and commonly used in transcriptomics, will be tested on artificial and real data. We will then test these techniques using a non-linear batch effect predictor currently in development in the lab to benchmark those approaches. Finally, we will try to use the fittest protocol to normalise our own data from the Leucegene project counting around 500 transcriptomes from different experimental origins.

Transcriptomics data normalisation is crucial, because it allows the usage of multiple datasets from multiple origins simultaneously without dreading the disastrous consequences of batch effects. This subject, although being a central point in bioinformatics, has not received enough attention in the past years and deserves to be addressed with urgently.

LAB TECHNIQUES

Bioinformatics
Python, Biopython, NumPy, SciKitLearn, Keras, and R
Statistics

FOR MORE INFORMATION

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

Internship project #12

Deep learning algorithms for precision medicine

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

PROJECT DESCRIPTION

The goal of this summer internship is to design a deep learning method for the integration of heterogeneous gene expression datasets to create a platform for joint analysis.

Transcriptomic analysis consists of a quantification of all expressed genes in the cell, resulting in a snapshot of the cell state. This highly versatile method shows great promise in the field of precision medicine. However, there are two radically different methods to quantify gene expression: microarrays and high-throughput sequencing. These methods yield different views of the same biological phenomenon and unfortunately also yield numerically incompatible results. Moreover, transcriptomic analyses are typically done in small sample sizes, especially when the subjects are human. It follows that for the same disease, quantifications will exist in both methods, which poses a problem of paramount importance when attempting to design precision medicine approaches, that usually benefit from large cohorts. Indeed, large cohorts offer a non-negligible gain in obtaining robust results as well as detecting rare biological events.

The first objective for the internship would be to explore unsupervised machine learning approaches for the integration of transcriptomic datasets from diverse quantification platforms. Then, the ultimate goal would be to create a Knowledge base that may integrate available clinical data for the analyzed samples.

LAB TECHNIQUES

Deep learning
Programming
Algorithms

FOR MORE INFORMATION

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

Internship project #13

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 #14

Bioinformatics of personalized targeted therapies against cancer

Under the supervision of François Major
RNA Engineering Research Unit

PROJECT DESCRIPTION

Our research program proposes a computer-assisted approach to analyze the genes expressed in a patient's cancer cells and design personalized targeted RNAi-based therapies that normalize gene expression in these cancer cells only. We are developing a pipeline in four steps. This project aims at applying and developing algorithms in two of these steps that relate to: i) the analysis of the RNA content of target cells; and, ii) the development of targeting strategies to address the phenotype transformation of cancer in these cells.

LAB TECHNIQUES

Multiple databases and multiple tools for RNA-seq data analysis
Systematic and integrative analysis of large gene lists
Graph analysis and visualization.

FOR MORE INFORMATION

iric.ca/en/research/principal-investigators/francois-major

Internship project #15

Calibrating protein output

Under the supervision of François Major
RNA Engineering Research Unit

PROJECT DESCRIPTION

The objective of this project is to calibrate the miRBooking software to predict protein output. MiRBooking is a software to determine miRNA interactions in the transcriptome and silencing effect on each gene. This project consists in: i) identify miRNAs binding specific genes at various expression levels in several cell lines using RIP-Seq experiments; and then, ii) experimentally measuring the actual efficiencies of these miRNAs on the expression of target genes' 3'UTR mutants using an inducible bi-fluorescent reporter system in endogenous contexts.

LAB TECHNIQUES

Molecular biology
MiRBooking
RIP-seq
RT-qPCR
Nothern blots
Reporter Genes
Fluorescence

FOR MORE INFORMATION

iric.ca/en/research/principal-investigators/francois-major

Internship project #16

Optimization of compounds as potential therapeutic agents

Under the supervision of Anne Marininer
Medicinal Chemistry 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 #17

Role of the atypical MAP kinase ERK3 in cancer progression

Under the supervision of Sylvain Meloche
Signalling and Cell Growth Research Unit

PROJECT DESCRIPTION

ERK3 and ERK4 define a distinct subfamily of atypical MAP kinases. These kinases display a number of structural, regulatory and functional characteristics that distinguish them from conventional MAP kinases like ERK1/2. Little is known about their regulation and biological functions. Recent findings from our laboratory suggest that ERK3 plays a key role in tumor progression by stimulating migration and invasiveness of cancer cells. High expression of ERK3 is associated with shorter metastasis-free survival and overall survival in breast cancer patients. We have identified a genetic program that links ERK3 signaling to a network of proteins associated with tumor metastasis. The objective of this project is to characterize the mechanism underlying the regulation of these gene targets by ERK3 and test their contribution to the tumorigenic process.

LAB TECHNIQUES

Molecular Biology
Cell Biology
RNA interference
CRISPR/Cas9 gene editing
Cell culture
Gene and protein expression studies
Protein phosphorylation experiments
In vitro assays of cell proliferation
Migration and invasion - in vivo metastasis assays
Mouse xenografts transplantations assays

FOR MORE INFORMATION

iric.ca/en/research/principal-investigators/sylvain-meloche

Internship project #18

Characterization of novel effectors of the Ras/MAPK pathway in cancer

Under the supervision of Philippe P. Roux
Cell Signalling and Proteomics Research Unit

PROJECT DESCRIPTION

The Ras/MAPK signalling pathway becomes activated in response to most growth factors and controls essential biological processes, including cell cycle progression, cell differentiation, survival and motility. Activating mutations in components of this pathway are frequently found in human tumours, such as in pancreatic (90%), colon (50%), thyroid (45%) and ovarian cancers (36%), as well as in melanoma (63%). Using proteomics approaches, we have identified several proteins that appear to be regulated by Ras/MAPK signalling, and are currently characterizing their roles in normal and cancer cells. The project will involve characterizing these proteins as potential novel effectors of the Ras/MAPK pathway, as they may be involved in tumorigenesis and represent novel therapeutic targets.

LAB TECHNIQUES

Cell culture
Transfection
Immunoprecipitation
Western Blotting
Mass Spectrometry Analysis
Other moleculare and cell biology approaches

FOR MORE INFORMATION

iric.ca/en/research/principal-investigators/philippe-roux

Internship project #19

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.

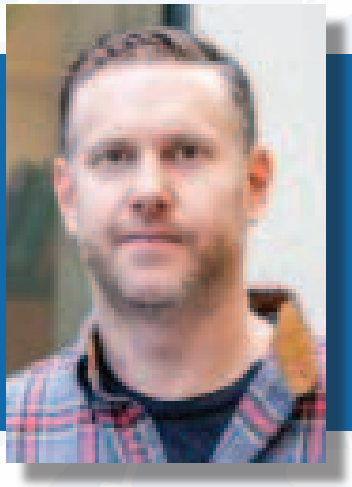
Along the way, recent genetic engineering technologies such as shRNA and CRISPR shall be implemented to knock-down additional transcripts of interest in various cell systems (cord blood cells, AML cell lines, primary AML cells) to assess their molecular functions in acute myeloid leukemia progression 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 #20

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

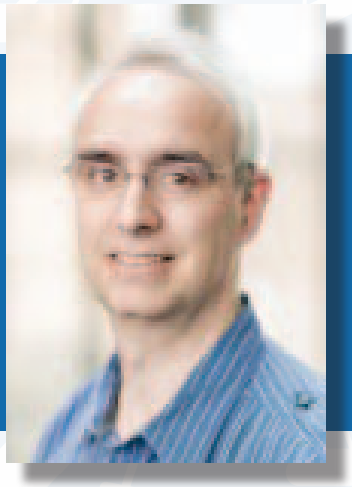
The RAS GTPases are fundamental regulators of normal development, causative agents in an extraordinary number of human cancers, and key determinants in several developmental disorders termed RASopathies. RAS proteins are encoded by three proto-oncogenes: HRAS, KRAS and NRAS. Of these, KRAS mutations 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

Molecular biology
Cloning
Protein biochemistry
X-Ray crystallography
Tissue culture

FOR MORE INFORMATION

iric.ca/en/research/principal-investigators/matthew-j-smith
matt19smith.wix.com/iric



Internship project #21

Characterization of new Ras/MAPK pathway components

Under the supervision of Marc Therrien
Intracellular Signalling Research Unit

PROJECT DESCRIPTION

The Ras/MAPK pathway plays a pivotal role in the control of cell proliferation and its aberrant up-regulation often leads to cancer. Signaling through the Ras/MAPK pathway depends on a number of core pathway components that include a module a three kinases known as RAF, MEK and MAPK. We have recently completed a genome-wide functional (RNAi-based) screen to identify additional factors modulating Ras/MAPK signaling. Intriguingly, while conventional signaling components were identified, we also observed that several hits played a role in controlling the steady-state levels of MAPK. In particular, we identified factors of the Ubiquitin/Proteasome System (involved in protein degradation) that control the half-life of MAPK. A position for a summer student is available in the laboratory for initiating the characterization of the mechanism of action of some of these new factors.

LAB TECHNIQUES

Plasmid constructs
DNA sequence analysis
CRISPR-based gene knockouts
Cell culture
Cell transfection
Protein immunoprecipitation
Protein separation on SDS-PAGE gels
Western blotting

FOR MORE INFORMATION

iric.ca/en/research/principal-investigators/marc-therrien

Internship project #22

Dynamic immunopeptidome and its significance in leukemia immunotherapy

Under the supervision of Pierre Thibault
Proteomics and Bioanalytical Mass Spectrometry Research Unit

PROJECT DESCRIPTION

Antigen presentation is essential for immune tolerance and immune responses against infectious disease and cancer. The activation of different cell signaling pathways can lead to significant changes in the antigenic presentation of neoplastic cells and the immune response. In this project, how changes in the abundance and composition of the peptide repertoire presented by the major class I histocompatibility complex (MHC I) are modulated in response to immunosuppressive drugs to better understand the antigenic presentation dynamics of lymphoblastic leukemia cells. The trainee will use various state-of-the-art approaches in immunology, affinity chromatography, proteomics and bioinformatics.

LAB TECHNIQUES

Cell culture
Microscopy
Affinity chromatography
Proteomics
Mass spectrometry

FOR MORE INFORMATION

iric.ca/en/research/principal-investigators/pierre-thibault

Internship project #23

A novel strategy for discovery of sirtuin inhibitors

Under the supervision of Alain Verreault
Chromosome Biogenesis Research Unit

PROJECT DESCRIPTION

Our laboratory discovered a fascinating feature of eukaryotic chromosomes. During DNA replication, chromatin structure needs to be duplicated and this requires the incorporation of newly synthesized histones into nascent chromatin. We showed that virtually all the new histone H3 molecules deposited throughout the genome are acetylated at lysine 56 (H3-K56ac). We also demonstrated that both acetylation and deacetylation of histone H3-K56 promote cell survival in response to a broad spectrum of DNA damaging agents that are frequently used in cancer chemotherapy (Nature 436: 294; Curr Biol 16: 1280; Cell 134: 244; Mol Cell Biol 32: 154; Genetics 200: 185). The enzyme that deacetylates H3-K56, known as Hst3, is conserved in many human pathogens such as Candida and Aspergillus species. We showed that inhibition of Hst3 using nicotinamide, a form of vitamin B3, leads to catastrophic DNA damage and Candida albicans cell death (Nature Medicine 16: 775). Thus, inhibition of Hst3 represents a novel therapeutic avenue to treat fungal infections that are potentially life threatening in immunocompromised patients (patients undergoing cancer chemotherapy, organ or bone marrow transplantation).

Hst3 is a fungal-specific member of a large family of NAD+-dependent protein deacetylases known as sirtuins, which are conserved from bacteria to humans. Human sirtuins are appealing targets to treat a number of human conditions that include, among many others, cancer, cardiovascular and neurodegenerative diseases (Expert Opin Ther Patents 25: 5). Unfortunately the current high-throughput assays for discovery of sirtuin inhibitors suffer from important limitations. The aim of this project is to develop the tools necessary to design novel high-throughput screening assays for discovery of inhibitors of fungal Hst3 and human sirtuins.

LAB TECHNIQUES

Tools for genetic code expansion
Genetic engineering for production of acetylated proteins
Protein expression and purification
Design of high-throughput assays for drug identification

FOR MORE INFORMATION

iric.ca/en/research/principal-investigators/alain-verreault

Internship project #24

Functional and chemogenomic studies of pediatric acute myeloid leukemia

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

PROJECT DESCRIPTION

The Wilhelm lab has a focus on using high-throughput approaches to study genome biology, including transcriptional and epigenetic regulation in both normal and disease contexts. As a model for disease conditions, we study Acute myeloid leukemia (AML) in children which is a disease that occurs when hematopoietic stem cells acquire mutations that force them to proliferate and block the ability of cells to differentiate. In children, AML is typical found with specific chromosomal translocations (such as the t(9:11) fusion involving the MLL gene) and has amongst the worst survival rates of any pediatric cancer. We have developed a new model system that allows transform healthy human cord blood (CB) cells into human leukemias. By sequencing the RNA and DNA of these "model AMLs" along with patient tumors, we have discovered a set of ~40 genes are specifically up-regulated in MLL translocated AMLs. We are now trying to understand how these genes participate in leukemogenesis and which are essential through a gene-by-gene shRNA knockdown approach. When we see that the cells require specific genes, we characterize the activity of the gene in more detail using a number of different approaches. In addition, we are analyzing patterns of growth of AML cells in response to a chemical screen of several thousand compounds and correlating this with mutation and gene expression patterns in order to identify novel potential therapeutic targets.

LAB TECHNIQUES

Polymerase chain reaction (PCR)
Western blotting
Cell culture
Cell proliferation assays
DNA/RNA sequencing

FOR MORE INFORMATION

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