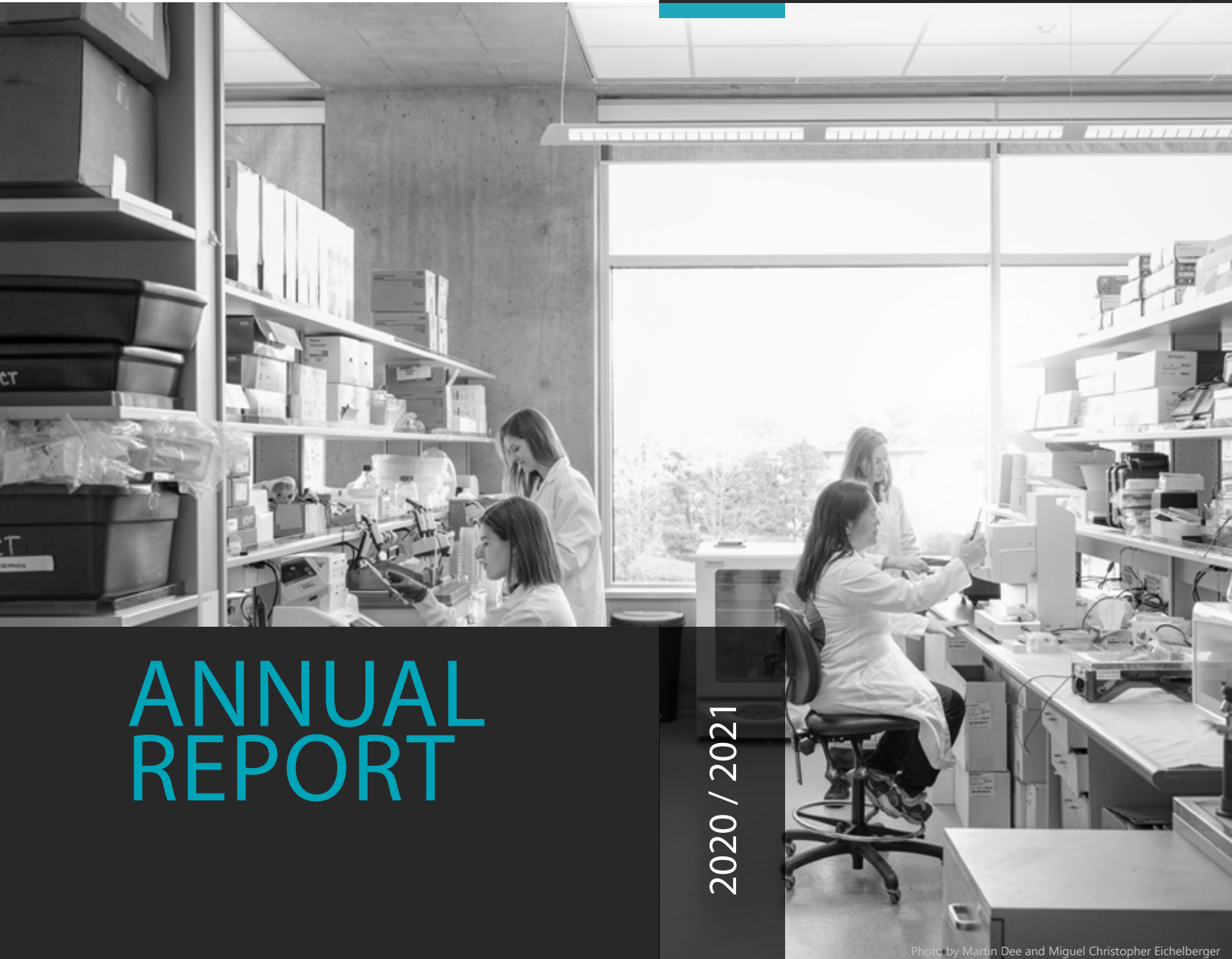




THE UNIVERSITY OF BRITISH COLUMBIA
Life Sciences Institute

www.lsi.ubc.ca



ANNUAL REPORT

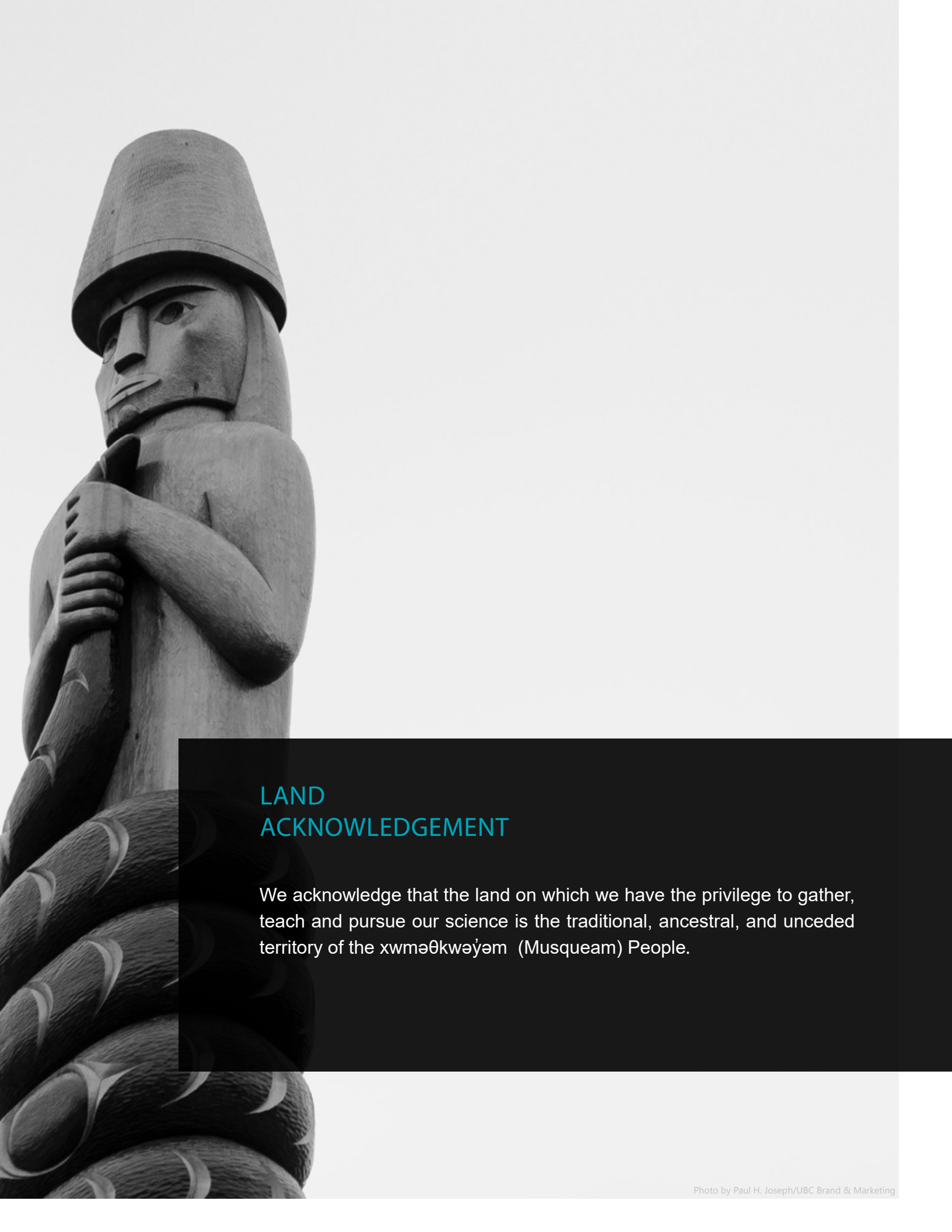
2020 / 2021

Photo by Martin Dee and Miguel Christopher Eichelberger



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Phone: 604.822.4128

INNOVATIVE,
INTERDISCIPLINARY SCIENCE.



LAND ACKNOWLEDGEMENT

We acknowledge that the land on which we have the privilege to gather, teach and pursue our science is the traditional, ancestral, and unceded territory of the xwməθkwəyəm (Musqueam) People.

ANNUAL REPORT

CONTENT

02

COMMENT FROM
THE DIRECTOR

03

ABOUT THE LSI

05

OUR
CONTRIBUTIONS
TO SCIENCE AND
SOCIETY

09

LSI BY THE
NUMBERS

10

MOST IMPACTFUL
PUBLICATIONS

15

FACULTY AWARDS &
ACHIEVEMENTS

16

TRAINING THE NEXT
GENERATION

17

TRAINEE AWARD
RECIPIENTS

21

FEATURED TRAINEE
PUBLICATIONS

24

SCIENTIFIC FACILITIES
& CORE SERVICES

25

ACKNOWLEDGEMENTS

26

APPENDIX:
FULL LIST OF
PUBLICATIONS



Photo by Paul H. Joseph / JBC Brand & Marketing



COMMENT FROM THE DIRECTOR

Science has become the art of our times, and scientists, the heroes and angels of the moment.

This report, spanning early 2020 through the first three months of 2021, illustrates our capacity to rise above and excel, despite the extraordinary challenges we have faced during this unprecedented period in our lives.

Our success rests on the efforts of many members of the LSI community. In early March, when curtailment was first imposed, we drew together and accomplished this quickly, competently, and smoothly. The LSI, the Life Sciences Centre (LSC) and the Centre for Blood Research (CBR) collaborated closely, receiving and addressing concerns and input, under the seasoned leadership of Drs. Ed Conway and George Mackie. Our department heads, the LSI/LSC team, wing managers, core and infrastructure staff, and others kept things running safely at LSI, all while continuing to do spectacular work through every stage leading towards fully resuming our activities.

The findings featured in this report represent the stunning progress and advances made in our science. As we have chosen to focus in detail on only 10 high impact publications where the primary effort came out of LSI labs, I would be remiss if I failed to mention the most renowned translational example of one of our own, and his role in the discoveries now protecting millions of lives. Dr. Pieter Cullis' work in lipid nanoparticles is the fruit of 40 years of groundwork leading to successful delivery of an mRNA vaccine in the midst of the ongoing pandemic.

Indeed, achievements across all disciplines within the Institute are keeping us ahead of the curve as a world-leading centre of excellence in the life sciences.

I am grateful for the tireless work of our new Deputy Director, Dr. Jim Johnson, who has joined me in leading the LSI at an enormously challenging time. He is laying the groundwork of transformation and working to deliver our vision of a dedicated space that will promote interaction, collaboration, and cross-pollination of ideas between trainees working in different areas. Breaking down the silos that divide us will propagate new and shared expertise in disciplines and techniques and drive our excellent science to even higher levels.

I do not exaggerate when I say the heroes and angels are amongst us, right here at the LSI, and UBC. It is a true privilege to work here among them. I am very proud of our collective scientific endeavor, our contributions toward reopening the world, and our work towards saving lives, livelihoods and our planet.

A handwritten signature in black ink, reading "Josef Penninger".

- Dr. Josef Penninger, Director

ABOUT THE LIFE SCIENCES INSTITUTE

The Life Sciences Institute is the premiere fundamental biological research organization at the University of British Columbia.

Since our launch 15 years ago, the LSI has become an innovation hub with global impact, poised on the continuum between basic and applied research.

Working together with colleagues across UBC, Canada, and the world, and learning from our collective experience conducting research responsive to society's biggest health and environmental challenges, the LSI looks to the future with fresh ideas and approaches as we claim our rightful place among the top foundational biological research institutes.

Our achievements rest on the efforts of more than 100 Principal Investigators (current and retired) and over 4,000 research trainees and staff from several UBC faculties and departments who conduct leading-edge, basic and preclinical research and translate their findings into treatments and environmentally sustainable solutions.

We undertake this vital work under nine major themes: blood research; diabetes; cell and neuroscience; and bacterial regulatory networks.



BACTERIAL ADAPTATION AND RESPONSE NETWORKS (BARN)

Group members investigate common molecular mechanisms bacterial adaptation and response to their diverse environments including the human host, oceans, forests, and soil. Expertise covers a range of disciplines, including biochemistry, bioinformatics, chemistry, genetics, genomics, microbial ecology, microbial physiology, and structural biology. <http://barn.lsi.ubc.ca>

CHEMICAL BIOLOGY OF DISEASE (CBD)

This multi-disciplinary team focuses on providing early-stage chemical agents for the treatment of a variety of disease-related pathologies including atherosclerosis, cancer, cardiovascular, immunological and infectious diseases. The group is comprised of biochemists, biophysicists, chemists, microbiologists, and molecular biologists. <http://cbd.lsi.ubc.ca>



NEUROSCIENCE RESEARCH GROUP (NEURO)

The mission of the Neuro Group is to further our understanding of how the nervous system develops and functions and how it is modified by injury, disease as well as genetic and environmental factors. LSI investigators study different levels of neural organization such as molecular/cellular, systems/circuit, behavioral/cognitive. <http://neuroscience.lsi.ubc.ca>



CELL AND DEVELOPMENTAL BIOLOGY (CELL)

Research covers a wide spectrum of cell and developmental biology, focusing on how cells integrate signals and develop into complex multicellular organisms and tissues. An overarching goal is to understand the mechanisms that direct cellular function and interactions during development and to determine how these may be disturbed in a wide range of diseases. Major interests in CELL include cellular junctions, protein trafficking and targeting, morphogenesis, cytoskeletal rearrangements, and signal transduction. <http://celldevelopment.ubc.ca>

INFECTION, INFLAMMATION AND IMMUNITY (I3)

This group focuses on how pathogens cause infections and how the body's immune system combats these infections. Research addresses how the immune system prevents disease, how immune system dysregulation can cause disease, and how manipulating the immune system could lead to new drugs and vaccines for curing or preventing infectious diseases, inflammatory and autoimmune diseases, and cancer. <http://iii.lsi.ubc.ca>



CARDIOVASCULAR RESEARCH GROUP (CRG)

The CRG studies how the heart generates and maintains its regular beat, and controls its force of contraction. Researchers focus on how dysfunctional ion channels lead to cardiac diseases. Expertise includes ion channel electrophysiology, molecular biology and protein structure, and models of cardiac disease. <http://crg.lsi.ubc.ca>

CENTRE FOR BLOOD RESEARCH (CBR)

The goal of the CBR is to improve the health and well-being of patients by performing innovative blood research. Researchers in this Centre use a broad range of leading edge basic science, biotechnological, engineering and clinical investigative approaches on blood and blood-related processes to improve health. <http://www.cbr.ubc.ca>



DIABETES RESEARCH GROUP (DRG)

Members of the Diabetes Research Group are studying diabetes from all angles. Their research aims to understand and treat multiple forms of diabetes including type 1 diabetes, type 2 diabetes and conditions associated with these diseases. Diabetes scientists in the LSI are working on projects focused on the fundamental causes of diabetes as well as novel strategies for treatment. A wide range of studies are ongoing, from investigations into the biochemistry of insulin signaling to the physiology of insulin release from pancreatic islets and much more. <http://diabetes.ubc.ca>

MOLECULAR EPIGENETICS RESEARCH GROUP

This group has a common interest in studying epigenetic gene regulation, namely how cells that have the same DNA can specifically regulate different expression patterns and how gene expression can be influenced without mutations in the actual DNA sequence. The most likely epigenetic processes include DNA modification, changes in histone modification, changes in chromatin structure, and changes involving non-coding RNA production and inheritance. <http://meg.lsi.ubc.ca>



These research groups provide our researchers with a framework to pursue common goals, share expertise and infrastructure, cross-pollinate between disciplines, and mentor students and highly qualified professionals.

In their collective pursuit of fundamental discovery science our scientists enjoy the intellectual freedom to flex their creative muscle and develop ideas or concepts that capture their curiosity in the absence of an immediate, obvious outcome or application. Yet it is from this untried ground that all innovations germinate, whether they are treatments for diseases, vehicles for COVID-19 vaccines, or sustainable approaches that harness the power of microbes to mitigate climate change, the only rival to the pandemic as the greatest challenge of our times.

OUR CONTRIBUTIONS TO SCIENCE AND SOCIETY



LEADING THE FIGHT AGAINST COVID-19

THE ACE2-SPIKE PROTEIN INTERACTION



Discovery of the cell entry mechanism that SARS-CoV2 uses

In the aftermath of the SARS epidemic, our Director Dr. **Josef Penninger** demonstrated a critical role for ACE2 as the cellular receptor for the SARS Coronavirus and linking ACE2 to lung failure in coronavirus infections. In 2020, these pioneering findings became critical and catapulted ACE2 to the most researched molecule globally as the cellular receptor of SARS-CoV2. The interaction between the SARS-CoV2 spike protein and ACE2 forms the basis for all COVID-19 vaccines and therapies including the only rational therapy—human recombinant soluble ACE2 (APN01), which resulted directly from Dr. Penninger's work, and is being tested further as an early intervention against severe COVID-19.

THE PFIZER/BioNTech VACCINE



Made possible by decades of lipid nanoparticle research

Our Former Director (2014-2017) Dr. **Pieter Cullis** has been working on drug delivery systems based on lipid nanoparticles for over 40 years. In 2020, technology originating from his LSI laboratory became the vehicle for the Pfizer/BioNTech COVID-19 vaccine, the first mRNA vaccine to be deployed at global scales and the fastest vaccine ever developed. Importantly, this made UBC one of only two universities world-wide to have made a significant contribution to this vaccine.*

*Gaviria, M. & Kilic, B. A network analysis of COVID-19 mRNA vaccine patents.
Nature Biotechnology 39, 546-548 (2021)

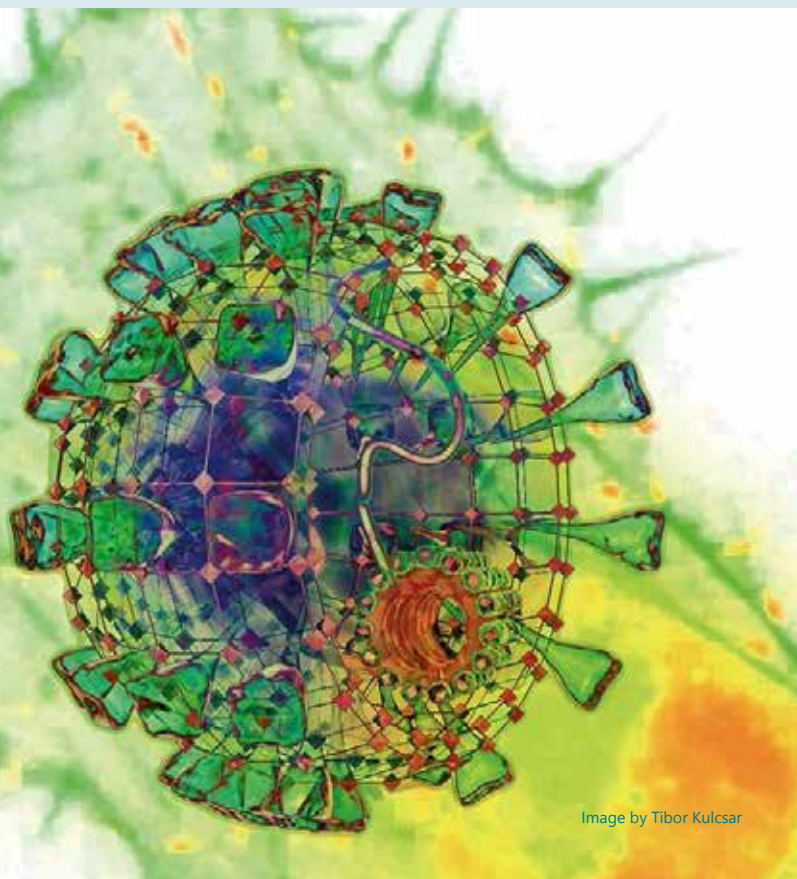


Image by Tibor Kulcsar

CRYSTALLOGRAPHIC STRUCTURE OF A SARS-COV-2 ENZYME



to aid antiviral therapeutic design

Dr. **Natalie Strynadka**, Tier 1 Canada Research Chair in Antibiotic Biology and Medicine, and colleagues resolved the X-ray crystallographic structures of Nsp5 the main protease (Mpro) of SARS-CoV-2 at 1.8 Å resolution. Mpro is linked to essential processing events for viral assembly and maturation. This structure is essential to delineating atomic details of the mechanistic pathway of SARS-CoV-2 replication in infected cells and can be used to optimize current inhibitor hits and design highly potent, novel Mpro inhibitors as life-saving antiviral therapy.

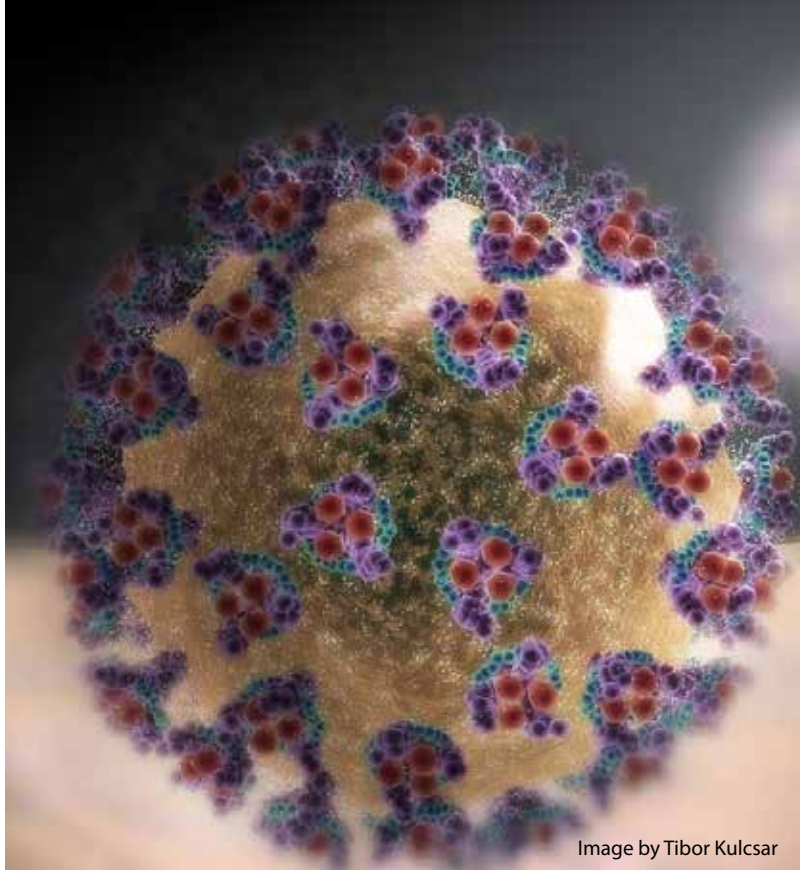


Image by Tibor Kulcsar



PROVIDING MECHANISTIC INSIGHTS TO COMBAT CANCER

NEW TOOLS



to identify cancer-causing mutations

A team led by Dr. **Christopher Loewen** and Dr. **Calvin Roskelley** recently combined high-content microscopy and artificial intelligence (AI) to devise a new method that can quickly and accurately predict the functional consequences of hundreds of genetic variants in cancer-associated genes. Genetic testing is the cornerstone of personalized medicine, and can reveal predisposition to hereditary diseases like cancer. However, there is often little to no clinical data for many of the gene variants identified — resulting in their classification as “variants of unknown significance” — and limiting their value. The new software toolkit they developed, Machine Assisted Phenotype Scoring (MAPS), is a low-cost, cloud-based, automated image analysis platform, part of a novel workflow analyzing changes in protein subcellular localization as an indicator of loss of function. Their method will allow researchers to quickly assess the function of genetic variants at scale, and help realize the full potential of personalized medicine in cancer.

A NEW ROLE FOR RANKL



in breast cancer

Dr. **Josef Penninger** made the groundbreaking discovery that the RANKL/RANK system plays a key role in preventing tumour development in triple negative BRCA1-driven breast cancer, opening up new possibilities for treatment of this aggressive and deadly disease. Years of basic research by Dr. Penninger's team into the RANKL/RANK interaction elucidated how the immune system functions in bone loss, founding a new field in osteoimmunology and leading to the development of denosumab, a monoclonal antibody targeting RANKL, used to treat bone loss in old age and in cancer patients. Now, based on Dr. Penninger's new findings, denosumab (Prolia®/Xgeva®) is in Phase III clinical trials for the prevention of BRCA1-driven breast cancer, underway in North America, Australia, and Europe, providing hope to hundreds of thousands of BRCA1 mutation carriers.

NEW CANCER IMMUNOTHERAPIES



Driving the development of next-generation treatments

Research led by Dr. **Kenneth Harder** and colleagues is driving the development of a next-generation cancer immunotherapy targeting myeloid cells in the immune system, which have been linked to suppression of anti-tumour immune responses. The team has formed a start-up, ME Therapeutics, to further develop their treatment, which is predicted to complement current immunotherapies and help overcome resistance in patients with refractory cancers. Their approach shows potential for treating multiple cancer types and will substantially impact cancer patient outcomes.

BREAKTHROUGHS IN DIABETES: RESEARCH TO TRANSLATION

STEM-CELL DERIVED CURE FOR DIABETES



at the global forefront

Drs. **Tim Kieffer** and **Jim Johnson**, working with several industry partners, have been at the global forefront of the effort for a stem-cell derived diabetes cure for almost a decade. Kieffer demonstrated the reversal of diabetes in animal models using embryonic stem cells differentiated into insulin-producing beta-cell lineage and pioneered the use of macro-encapsulation for cell containment. This technology is now in a first-in-human and first-in-class clinical trial. Kieffer and Johnson were the first in the world to report an advanced differentiation protocol that resulted in cells capable of glucose-induced insulin secretion in culture, and rapid reversal of diabetes in rodents following transplant.

BLOOD VESSEL ORGANOIDs TO STUDY DIABETES



a new model for the study
of blood vessel changes

Dr. **Josef Penninger** developed the world's first self-organizing 3D human blood vessel organoids from embryonic stem cells, which faithfully recapitulate the structure and function of human blood vessels and are amenable systems for modelling and identifying the regulators of diabetic vasculopathy, a disease affecting hundreds of millions of people globally. As the Canadian lead on a UK-Canada Diabetes Research Team, Dr. Penninger will use his organoid model to investigate the potential of two previously identified molecules to reverse blood vessel changes caused by high blood sugar in diabetes. This research is expected to accelerate discovery of new treatments for blood vessel complications in diabetes.



TACKLING TUBERCULOSIS: A GLOBAL HEALTH SECURITY THREAT

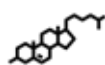
NEW TREATMENTS FOR INFECTIOUS RESPIRATORY DISEASES



combatting drug-resistant bacteria

Tuberculosis (TB) is one of the most devastating infectious diseases, causing ~10 million new infections and 2 million deaths each year. The emergence of multidrug-resistant strains of the bacteria that causes TB has created an urgent demand for new and better treatments. Dr. **Yossef Av-Gay** has developed specialized intracellular high-throughput screening assays to identify several novel anti-TB compounds active in human macrophages, focusing particularly on host-directed therapies as a strategy to avoid bacterial evolution of resistance. They have previously also shown efficacy of nitric oxide (NO) as an antimicrobial agent, leading to the foundation of Beyond Air (XAIR on NASDAQ), now developing treatments for bronchiolitis, viral infections, and cystic fibrosis based on his work.

TARGETING CHOLESTEROL CATABOLISM



to treat tuberculosis

Tier 1 Canada Research Chair in Microbial Catabolism and Biocatalysis, Dr. **Lindsay Eltis** has made seminal discoveries that advance our understanding of steroid catabolism by several bacteria including the pathogen of tuberculosis, *Mycobacterium tuberculosis* (Mtb). This includes – elucidation of a pathway conserved in all known steroid-degrading bacteria by which they degrade the last two steroid rings; characterization of a novel ring-opening enzyme, *lpdAB*, which is required for the virulence of Mtb; and establishing that the ability of Mtb to catabolize host-derived cholesterol is essential to the pathogen's virulence and that targeting cholesterol catabolism in Mtb is a promising therapeutic strategy. Based on these fundamental discoveries Dr. Eltis is collaborating with academic and industry partners to develop two classes of compounds as treatment and validating additional therapeutic targets in the cholesterol catabolic pathway.

LIFE SCIENCES INSTITUTE BY THE NUMBERS



INTERDISCIPLINARY MAKEUP

10

DEPARTMENTS

5

FACULTIES



GRANTS

\$40,431,083

RECEIVED IN FUNDING



RESEARCHERS

83

PRINCIPAL
INVESTIGATORS

756

HIGHLY QUALIFIED
PERSONNEL



TRANSLATION

17

ACTIVE SPIN-OFFS



PUBLICATIONS

221

IN 2020-2021

TEN IMPACTFUL PUBLICATIONS



BLOOD CIRCULATION OF A NOVEL NANOPARTICLE PROVIDES INSIGHTS ON HOW THE IMMUNE SYSTEM READS NANOMATERIALS

Lipid nanoparticles (LNPs) made the jump from scientific journals to public awareness in a matter of months as the mechanism delivering mRNA vaccines into millions of people's arms around the world.

While this delivery system enabled protection levels beyond any initial expectation, LNPs are only one means of introducing therapeutics via nanomaterials into the blood stream. Nanomedicine's potential is tremendous, but unlocking its possibilities requires significant work to identify and mitigate any potential toxicity. The interaction between the immune system and nanomaterials is the focus of an important study led by Centre for Blood Research investigator **Jayachandran Kizhakkedathu**, with UBC and international collaborators published in [Nature Communications](#). [Read more](#)



INTERFERON STUDY PROVIDES GLOBAL VIEW OF THE COMPLEX CELLULAR NETWORKS ACTIVATED IN IMMUNE RESPONSE

The type I interferon (IFN) response is an ancient pathway in the body's armamentarium against viruses. This defense, on a cellular level, involves inducing transcription of hundreds of IFN-stimulated genes. Using biochemical and transcriptomic approaches, IFN-stimulated genes have been thoroughly catalogued across multiple species and cell types. But their antiviral mechanisms have not been fully characterized.

Using a combination of quantitative proteomic approaches, Biochemistry and Molecular Biology researchers **Eric Jan** and **Leonard Foster** shed light on these mechanisms by investigating the effects of IFN signaling on the human proteome, and mapping how IFN induces rearrangements in the protein-protein interaction network in humans in a study published in [Genome Biology](#). [Read More](#)



INSIGHTS INTO THE MECHANISMS THAT CONTROL BLOOD DEVELOPMENT AND IMMUNE RESPONSE

Stem cells and their potential impact on human health hold fascinating possibilities for repair and regeneration. They also play essential roles in the capacity to fight infections. Blood stem cells are the linchpin in this process, prompting living organisms to produce immune cells. However, the intricacies and regulation of infection-triggered conversion of blood stem cells to cells with immune function is not well understood.

Dr. **Guy Tanentzapf**, a Cellular and Physiological Sciences researcher in the LSI focuses on the role played by the cellular environment, or extracellular matrix, in the regulation of stem cells and its micro-environment. In a study in [Current Biology](#), Dr. Tanentzapf and his team, led by first author Dr. **Rohan Khadilkar**, explored the impact of external cues in the extracellular matrix, or ECM, on integrins—the main family of adhesion receptors that function as molecular fingertips that sense the environment and then facilitate signalling inside the cells. [Read More](#)



RADICAL AND ELEGANT GENE TRANSCRIPTION FINDINGS OVERTURN EXISTING THEORY ON HISTONE ACETYLATION

Approximately two metres of DNA is packaged into the nucleus of a single human cell. This process is facilitated by a class of proteins known as histones that, akin to spools of threads, compact the DNA into a compartment that is only 0.00002-0.00004 metres in diameter. Only a fraction of the human genome codes for proteins, the basic building blocks of cells, and storing the remaining DNA in an inaccessible form is important for correct gene expression, genome stability, and protection of cells from the dangerous effects of the parasitic retroviral DNA elements that make up much of the human genome. Cells are therefore challenged with the task of keeping part of the genome in an active and accessible state, while maintaining the remainder as inactive and inaccessible.

A key pathway for regulating chromatin structure is the neutralization of positively charged amino acids within histones, a process called histone acetylation. This modification weakens histone contacts with the negatively charged DNA, allowing cellular machinery to access the underlying DNA. Consistent with this, a tight correlation between histone acetylation and gene activation has been confirmed by a large body of evidence. The importance of histone acetylation for normal cell function is underscored by the fact that many disease-causing mutations have been mapped to genes encoding histone acetyltransferases (HATs) and histone deacetylases (HDACs), the enzymes that add or remove this modification, and drugs targeting these enzymes show promise for treatment of a wide range of disorders.

The destabilizing effects of acetylation on chromatin structure have led to a general assumption about the sequence of events: that acetylation occurs before gene transcription. A “radical and elegant” study published in [Nature Communications](#) by Drs. **LeAnn Howe** (Biochemistry & Molecular Biology) and **Matthew Lorincz** (Medical Genetics) suggests that this is not the case. Using immunoblot and chromatin immunoprecipitation-sequencing in budding yeast cells, the researchers clearly show that the bulk of histone acetylation depends on transcription and does not precede it. This dependency is explained by the need for RNA polymerase II to disrupt chromatin, allowing HATs to access their histone substrates. This research challenges the existing dogma that histone acetylation is simply part of the gene activation process, and instead suggests that acetylation is a component of a feed forward loop that maintains active gene expression states.



USING CRYO-EM AS A STRUCTURAL SLEUTH TO IDENTIFY TARGETS FOR TREATING A RARE DISEASE: MALIGNANT HYPERTHERMIA

Malignant Hyperthermia (MH) is an anesthetist’s nightmare, and the source of wrenching loss to thousands of families.

Before it was well understood, up to 90 percent of people who carried a mutation in the ryanodine receptor in RyR1, a protein linked to skeletal muscle, died when exposed for the first—or a subsequent time—to volatile (inhaled) anesthetic.

Patients lead fairly normal lives, until there is a trigger. MH episodes are brutal: muscles can go rigid and temperatures can soar up to 43C. If not treated immediately with the right drug, the patient will die.

Dr. **Filip Van Petegem**, a professor of Biochemistry and Molecular Biology, studies mutations of the ryanodine receptor, a daunting channel protein noted for its size and complexity. In a paper published in [Nature Communications](#), Van Petegem and colleagues showed the sequence variations associated with MH cause large changes in the structure of the RyR1 protein, which make it easier for this channel to open.

This opening allows calcium ions to flow between the compartments of the cell, where the increased concentration of calcium signals functions such as gene transcription, proliferation and cell migration. In muscle cells, this flow triggers contraction. [Read More](#)



SEX-BASED DIFFERENCES IN METHYLATION SO STRIKING - MALE AND FEMALE GERM CELLS LOOK AS IF THEY ORIGINATE FROM DIFFERENT SPECIES

One of the lingering epigenetic mysteries in germ cell biology is: how can sperm and eggs of the same species have DNA methylation profiles so different from, one another? In a study published in [Nature Genetics](#) Dr. **Matthew Lorincz** and Dr. **Kenjiro Shirane** uncover the underlying basis of “a significant fraction” of sex-based DNA methylation differences, demonstrating that male and female germ cells use related, but distinct histone methyltransferases to direct DNA methylation across the genome.

Only 40 percent of the genome is methylated in mouse oocytes (eggs), whereas over 80 percent of the genome is methylated in mature sperm. The molecular basis of these sex-based differences in *de novo* DNA methylation remains an enigma. In this study, using conditional knockout mice and next generation sequencing approaches to study the transcriptome and epigenome, the researchers show that distinct histone H3 lysine 36 (H3K36) methyltransferases (KMTases) play instructive roles in *de novo* DNA methylation in mouse oocytes and sperm.

Lorincz, Shirane and their collaborators have been working for several years to dissect the interplay between histone modifications and DNA methylation, using the mouse as a model system. Until their 2020 work, the role of histone marks in guiding DNA methylation in the male germline was unknown. [Read More](#)



NEW RESEARCH HIGHLIGHTS THE IMPORTANCE OF A FORGOTTEN ORGAN IN ENSURING HEALTHY PREGNANCIES

An international research team led by Dr. **Josef Penninger** uncovered for the first time the importance of a small gland tucked behind the sternum that works to prevent miscarriage and diabetes in pregnant women. The organ in question is the thymus, identified in a study published in *Nature* as playing a significant role in both metabolic control and immunity in pregnancy.

How the immune system adapts to support mother and fetus has puzzled researchers for decades. The study, published in [Nature](#), revealed that female sex hormones instruct important changes in the thymus, a central organ of the immune system, to produce specialized cells called Tregs to deal with physiological changes that arise in pregnancy. The researchers also identified RANK, a receptor expressed in a part of the thymus called the epithelium, as the key molecule behind this mechanism. Previously, its role in pregnancy was not known. To get a better understanding, the researchers studied mice where RANK had been deleted from the thymus. They found that the absence of RANK prevented the production of Tregs in the thymus during pregnancy. This resulted in fewer Tregs in the placentas, leading to elevated rates of miscarriage. [Read more](#)



CHARACTERIZATION OF ALKYLGUAIACOL-DEGRADING CYTOCHROMES P450 FOR THE BIOCATALYTIC VALORIZATION OF LIGNIN

Climate change and the shortage of fossil-derived gas and oil are driving thirst for renewable resources. Interest is growing in the lignin in forestry and agricultural waste streams, as this aromatic polymer has tremendous untapped potential as a source of high-value products, including carbon fiber, commodity chemicals, and fuels.

As the second-most abundant biopolymer on earth after cellulose, an estimated 100 million tons of lignin is produced annually. Effective processing methods have advanced slowly, but new opportunities for upgrading lignin are accelerating as the result of research into fractionation technologies and the engineering of microbes to convert lignin into a useable form.

An interdisciplinary collaboration between Microbiology and Immunology researchers Dr. **Lindsay Eltis** and Dr. **William Mohn** is playing an important role in this emerging area. In a significant 2020 publication in [PNAS](#), the team identified a novel microbial pathway for breaking down alkyl guaiacols - fragrant liquid and/or solid materials derived from several types of industrial lignins. [Read More](#)



A NEW ASSAY AND MACHINE LEARNING UNCLOAK THE CANCER-CAUSING POTENTIAL OF VARIANTS OF AN IMPORTANT TUMOR SUPPRESSOR GENE

As genetic testing becomes more routine, genetic variations are being identified in the population faster than ever. For disease-associated genes, this scenario makes it imperative that scientists differentiate between benign and disease-causing variants, so that treatment can begin, or a patient's status can be understood, and monitored.

People with disease-causing variants of PTEN, a tumor suppressor gene, will develop hamartoma tumor syndrome, a spectrum of conditions associated with multiple cancerous or benign tumors. Although the enzymatic function of PTEN and the consequences of a number of its tumor-linked mutations are known, there is little or no information about many recently identified clinical variants.

In a study that made the July 2020 cover of the journal [Cancer Research](#), Cellular and Physiological Sciences researchers Dr. **Calvin D. Roskelley** and Dr. **Christopher J.R. Loewen** addressed this gap by developing a cell-based assay that uses a premalignant cell line derived from the thin layer of tissue that coats and lines the surface of the milk ducts in the breast. These human mammary epithelial cells were deficient in PTEN. [Read More](#)



ATOMIC BLUEPRINTS PROVIDE VALUABLE SUPPORT IN DESIGN OF MECHANISM-BASED ANTIVIRALS TO COMBAT COVID-19

As COVID-19 ravaged the planet, a small group of investigators at the LSI pivoted their research, and began working at full tilt to identify ways to cripple the SARS-CoV-2 virus.

Biochemistry and Molecular Biology researcher Dr. **Natalie Strynadka**'s lab was one of four at the Institute to receive support in an early round of federal funding aimed at rapid response to the urgent need for treatment. As the director of the High Resolution Macromolecular Electron Microscopy facility at the Institute, where her research includes a focus on the structure of inhibitors that block antibiotic-resistance, she set her sights on finding a way to block replication of SARS-CoV-2. Her team's target was Main Protease (Mpro), an enzyme produced by the virus.

When SARS-CoV-2 infects cells, it starts producing new viral proteins to make more viruses. Initially, a long chain of "polyproteins" is produced from the viral genome, which need to be cut (cleaved) off into individual functional units. In the absence of this essential processing by proteases, including Mpro, the virus cannot replicate. This makes proteases an attractive target for the rapid development of antiviral drugs. Proven drug therapies for other global viral pathogens, such as HIV, also target central proteases.

In a paper published in [Nature Communications](#), the team revealed how Mpro binds the protein it cleaves (its substrate) to provide important clues as to how it works and how best to design drugs to block its action. [Read More](#)

FACULTY

AWARDS AND ACHIEVEMENTS

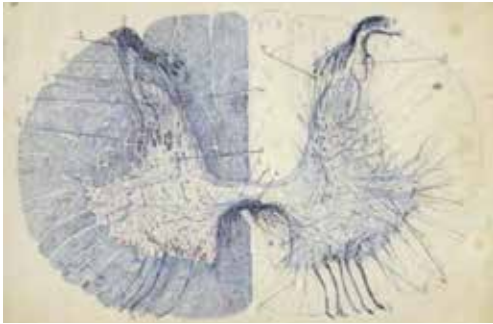


Image from the Archivio Fernando Castro, used as an illustration for the 12th FENS Forum of Neuroscience in Glasgow UK, 11 July 2020.

KAREN CHEUNG

Dept of Electrical & Computer Engineering, School of Biomedical Engineering

was [elected as a fellow by the American Institute for Biological Engineering](#), one of the highest professional distinctions in biomedical engineering.

DANA DEVINE

Depts of Biochemistry & Molecular Biology, Pathology & Laboratory Medicine, Director, Centre for Blood Research

received the International Society for Blood Transfusion's President's Award and became president-elect of the AABB (formerly known as the American Society of Blood Banks).

JAYACHANDRAN KIZHAKKEDATHU

Depts of Chemistry, Pathology & Laboratory Medicine, Centre for Blood Research, UBC School of Biomedical Engineering

was [named a Fellow, Biomaterials Science and Engineering](#) by the International Union of Societies for Biomaterials Science and Engineering.

ELIZABETH RIDEOUT

Dept of Cellular & Physiological Sciences

was named [CIHR Sex and Gender Science Chair in Genetics](#).

CAROLINA TROPINI

Dept of Microbiology & Immunology, School of Biomedical Engineering

was [named a Distinguished Investigator by the Paul G. Allen Frontiers Group](#). Dr. Tropini was also recognized as a Johnson & Johnson Scholar and [winner of the 2020 Johnson & Johnson Women in STEM2D Scholars Award](#) in the field of Engineering, as well as a [2019-2021 CIFAR Azrieli Global Scholar](#).

MARK CEMBROWSKI

Dept of Cellular & Physiological Sciences

was appointed a member of the Cajal Club, and the recipient of this year's [Krieg Cortical Explorer Award](#). Dr. Cembrowski was also recognized with a [Michael Smith Foundation for Health Research 2020 Scholar Award for early investigators](#) and was named a [2019 Brain Canada Azrieli Foundation Future Leader in Canadian Brain Research](#)

ED CONWAY

Dept of Medicine, Centre for Blood Research

received a [2020 UBC Science Co-op Supervisor Recognition Award](#), recognizing the outstanding mentorship and coaching he provides to co-op students.

RACHEL FERNANDEZ

Dept of Microbiology and Immunology

was [appointed UBC Associate Vice-President, Research and Innovation](#), effective March 15, 2021. Fernandez joined Dr. Murphy and Associate Vice-Presidents, Research and Innovation, Dr. Matthew Evenden and Dr. Phil Barker in sharing leadership of a diverse range of portfolio units and initiatives that support UBC's research and innovation activities.

JOY RICHMAN

Dept of Oral Health Sciences

was honoured by the Canadian Association for Dental Research (CADR) and the Association of Canadian Faculties of Dentistry (ACFD) with a [national award honouring outstanding dental research faculty](#).

KENJI SUGIOKA

Dept of Zoology

was [named a recipient of a Michael Smith Foundation for Health Research 2020 Scholar award](#). The program is designed to support early career researchers in establishing research careers.

OUR STRENGTH IN TRAINING THE NEXT GENERATION

[Read an interview with Lianna Watt, pictured here with her supervisor, Dr. Elizabeth Rideout.](#)

Photo by Kerry Blackadar

IT IS OUR RESPONSIBILITY

to prepare the scientists who will shed light on the unanswered and unanswerable questions that we cannot yet resolve. From undergraduate to postdoctoral levels — from atoms to molecules — to organisms and their environment, we are dedicated to preparing our students, colleagues and highly qualified professionals to extend the frontiers of science beyond our times.

Above all, we believe that research is foremost about people - people who entrust us with their hopes and resources to improve health, quality of life, and societal resilience through our science and people who conduct and support the scientific research that leads to new knowledge and solutions.

TRAINEE

AWARDS AND ACHIEVEMENTS

LSI PHD STUDENTS RECOGNIZED WITH TOP NATIONAL AWARDS

PhD candidates Peter Grin and Jerry Leung were 2020 recipients of the prestigious Frederick Banting and Charles Best Canada Graduate Scholarship Doctoral Award, which is granted to high-calibre doctoral students at Canadian institutions.



Jerry Leung (Cullis Lab) studies the use of lipid nanoparticles (LNPs) to modify and enhance platelet function as a novel cell therapy, which has immediate applications towards the treatment of particular blood disorders and related conditions. He hopes to develop a useful research tool and contribute to the generation of more effective blood transfusion products for hemorrhage control and the treatment of other diseases which platelets might modulate.

Peter Grin (Overall Lab) studies an important protein involved in regulating the levels of LDL-cholesterol in the blood, and how this protein, called PCSK9 is processed by a particular family of protease enzymes, and also looks at the functional biological effects of this processing on the development of heart disease or stroke. During the pandemic the Overall lab transitioned to studying proteases made by the SARS-CoV-2 virus, and Peter became increasingly involved in efforts to unravel biology related to SARS-CoV-2 proteases.

[Read more](#) about our Banting scholars



PRIYE IWORIMA WINS A GOLD AWARD IN CHSRF'S 2020 POSTER COMPETITION

Priye Iworima, a PhD student in the Kieffer Lab received a Canadian Student Health Research Forum Gold Award for her poster presentation in the 2020 competition. Graduate programs focusing on health research across the country are asked each year to nominate their top doctoral trainee to attend CSHRF, and Iworima was nominated by the School of Biomedical Engineering at UBC. CHSRF awards celebrate trainees based on their excellence in, and contributions to, healthcare research. During the course of the CHSRF event, participants compete in the Canadian Institute of Health Research National Poster Presentation, attend the University of Manitoba's Gairdner Symposium, and have the opportunity to network with other exceptional graduate trainees and Gairdner Laureates. Iworima was one of 177 trainees to compete, and was recognized for her pursuit of a cure for type-1 diabetes, a condition characterized by chronic high blood sugar due to a deficiency of insulin from the pancreatic islets.

Diabetes can be reversed through cell transplantation, but its widespread use as a form of insulin replacement therapy is limited by the scarcity of donor islets. Iworima's research is exploring the use of stem cells as an unlimited source of insulin-producing cells to treat diabetes. Together with colleagues in the Kieffer Lab, she is using a stepwise protocol to convert the stem cells into insulin producing pancreatic islets. The researchers are optimizing this cell culture protocol while also investigating procedures that will permit large-scale manufacturing of stem cell-derived islet cells. Ultimately, they hope that these cells can be used to effectively treat diabetes.

Listen to an interview with Priye Iworima on ["From Beta Cells to Bicycles"](#), the BC Diabetes Network's podcast. Learn more about the research being done in the Kieffer lab by [clicking here](#) and following Priye on [Twitter](#).



2020 MICHAEL SMITH FOUNDATION FOR HEALTH RESEARCH AWARDEE FOCUSES FELLOWSHIP ON RARE ARRHYTHMIAS



Dr. Alison Yueh Li made the jump from a doctorate focusing on genetic mutations in cardiac hypertrophic cardiomyopathy at Simon Fraser University to a Michael Smith Foundation Health Research Traineeship Awardee in the Van Petegem Lab at the outset of the pandemic.

As one of 43 exceptional BC health researchers selected by the Foundation that year, Li's fellowship work will continue to centre on the heart, but will move to the notably large and complex ryanodine receptor (RyR2). Working alongside Dr. Filip Van Petegem, and in collaboration with her former PhD supervisor Dr. Glen Tibbits, she is developing novel therapeutic targets to treat arrhythmia-causing variants in the ryanodine receptor.

The MSFHR award will provide the opportunity to explore the link between mutations in RyR2 (the cardiac isoform) and stress-induced cardiac arrhythmia. These arrhythmias are of particular clinical interest, because they cause CPVT (catecholaminergic polymorphic ventricular tachycardia), placing people with RyR2 mutations at risk for sudden cardiac death. Dr. Li is using cryo-electron microscopy to see how the mutations affect the structure of RyR2.

Read about [Dr. Li's MSHRF-funded fellowship](#)

A FULBRIGHT SCHOLAR AND A WALTER BENJAMIN AWARDEE JOIN THE CEMBROWSKI LAB



A spring 2020 graduate in biology from the University of Oregon, **Rennie Kendrick** joined the laboratory of Assistant Professor Dr. Mark Cembrowski on a prestigious Fulbright scholarship in January, 2021.

Kendrick has been developing and applying big-data experimental paradigms to study the cellular and molecular basis of fear memory in the brain. While she has known for a long time she would pursue a career in research, Kendrick wanted to take some time off before going to graduate school to get additional research experience. The opportunity to model biological systems in big data was a major draw to Vancouver.

Kendrick completed her degree in biology at the University of Oregon Clark Honors College, working as a research assistant in the labs of Dr. David McCormick and Dr. Dasa Zeithamova. Her honors thesis work in Dr. Zeithamova's lab aimed to identify learning conditions that enhance associative memory and promote memory integration.

[Read more about Rennie Kendrick](#)

A "lucky and perfect fit" for Walter Benjamin award winner

Dr. **Larissa Kraus**, a Walter Benjamin Fellowship awardee came to the Cembrowski Lab to work on a collaborative project that harnesses her experience with human brain tissue and her interest in epilepsy.

She began working with resected living human brain tissue during her PhD at the Charité in Berlin as part of an investigation of novel anti-epileptic mechanisms. A meeting between her supervisor and Dr. Cembrowski identified potential synergies between Kraus's work and Cembrowski's techniques and expertise with single cell RNA sequencing. In short order, Kraus and Cembrowski decided to do a project together, which builds on Kraus's interests in epilepsy, its causes and treatment and leverages her experience with living tissue. Identifying new therapeutic options for temporal lobe epilepsy is important to Kraus, given that 30-40% of patients with this condition continue to have seizures despite taking multiple anti-epileptic drugs.

[Read more about Dr. Kraus](#)



Photo by Paul H. Joseph/UBC Brand & Marketing

JORDAN J. SHIMELL RECEIVES A BRAIN STAR AWARD FOR WORK UNDERSTANDING X-LINKED INTELLECTUAL DISABILITY

The Canadian Association for Neuroscience (CAN) announced winners of the prestigious Canadian Institutes of Health Research's Institute of Neurosciences, Mental Health and Addiction (CIHR-INMHA) Brain Star Awards in August of 2020. Dr. **Jordan Shimell**, a former PhD student in the Bamji Lab, was one of the 16 recipients selected from across the country.

Brain Star awards are given to students and trainees who have published high impact discoveries in the fields and disciplines covered by the INMHA. Shimell was recognized for his work studying the role of the enzyme ZDHHC9 in brain connectivity. His results showed that ZDHHC9 regulates neuron growth, as neurons lacking ZDHHC9 had shorter, less complicated dendrites, which are the branches of neurons that receive inputs from other cells. Shimell's work also showed that ZDHHC9 modified the balance of excitatory and inhibitory synapses formed onto these cells, specifically through a mechanism leading to a reduction in inhibitory synapses. These findings further our understanding of the role of palmitoylation in the nervous system and may provide the foundations for therapeutic interventions for patients with alterations in ZDHHC9 function.

Dr. Shimell's work offers new clarity on the role of ZDHHC9 at the cellular level and its implications for circuit development. The findings also offer a plausible mechanism for how loss of ZDHHC9 might contribute to intellectual disability and epilepsy. A related publication in *Cell Reports*, "The X-linked intellectual disability gene *Zdhhc9* is essential for dendrite outgrowth and inhibitory synapse formation," was based on Shimell's PhD thesis. He is now a scientific recruiter for STEMCELL Technologies.

[Read more about Dr. Shimell](#) and his work. [Read the paper.](#) This research was supported by the Canadian Institutes of Health Research



LIANNA WAT SWEEPS CIHR GOLD, A GAIRDNER, AND WILL GO TO THE 2023 LINDAU NOBEL LAUREATE MEETING



LSI PhD student **Lianna Wat** prevailed over the top 5% of Canada's doctoral students conducting health research to sweep three prestigious accolades including the Lindau Award at the 2020 virtual Canadian Student Health Research Forum (CSHRF).

Now in her final year working with Dr. Elizabeth Rideout, Wat was the first-ever student put forward by the Cell and Developmental Biology program, her home department.

During the course of the CSHRF event, participants compete in the Canadian Institute of Health Research (CIHR) National Poster Presentation, attend the University of Manitoba's Gairdner Symposium, and have the opportunity to network with other exceptional graduate trainees and Gairdner Laureates. This year, 177 trainees competed in the CIHR National Poster Presentation. The top six trainees from the CIHR National Poster Presentation competition are then selected for a second round of judging conducted by Gairdner Laureates to determine Gairdner Student Award recipients and the Lindau Award recipient—the CSHRF only awards one Lindau Award per year.

A ten-slide online presentation of Wat's PhD project captured the attention of the judges, who are all Gairdner Laureates. Wat presented her work on a gene called *brummer*, which encodes a protein equivalent to mammalian ATGL, and its role in male-female differences in fruit fly fat storage and breakdown. The goal of the project is to understand how males and females regulate fat metabolism differently as this knowledge will aid in the development of more effective treatments for metabolic diseases in both sexes

Due to finish her doctoral work by the end of 2021, Wat weighed a post-doctoral fellowship, vs pursuing an MD degree. She will be pursuing a fellowship at Stanford, with Dr. Katrin Svensson. [Read more about Lianna Wat and her research.](#) [Read about the Lindau Meetings in 2020.](#)

FEATURED TRAINEE PUBLICATIONS

LSI PHD STUDENT DEVELOPS NEW TOOL FOR STUDYING THE ROLE OF GENES OF INTEREST IN BETA-CELLS AND DIABETES

Adam Ramzy, a third-year year medical student at UBC, helped develop a novel gene therapy tool that can act as a “trojan horse” to selectively deliver Cre to beta-cells in the pancreas.



An MD/PhD student in Kieffer Lab since 2014, Ramzy was first author on a 2020 study published in Nature Research Scientific Reports. The study is one of the chapters of his thesis, alongside other work on insulin-producing beta-cell development and function.

Conventionally, expression of Cre in specific cells required use of special genetically modified mice that are extremely costly and time-consuming to generate. In their study, Ramzy and colleagues present an alternative: a novel gene therapy tool that can act as a “trojan horse” to selectively deliver Cre to beta-cells in the pancreas. In this study, they demonstrate the utility of the tool by studying the impact of loss of the insulin gene on beta-cell identity. This tool will be broadly useful to researchers in the field of diabetes for studying the role of genes of interest in beta cells. It is being used in multiple ongoing projects within the Kieffer lab. [Read More.](#)

MD/POSTDOC BRINGS INSIGHTS FROM CANCER CLINIC TO CONSIDERATION OF AUTOIMMUNE ROLE IN SEVERE COVID-19

During a rotation in Zurich Dr. **Omar Hasan Ali** encountered patients with severe COVID-19 who had the same thrombosis localized in their toes that he and his mentor were used to seeing in their cancer patients. The mentor, Dr. Lukas Flatz, a professor of dermatology, had a flash of inspiration based on clinical experience with other autoimmune reactions, when the body attacks its own tissues. In this case, the blood clots and purplish toes seen in COVID-19 reminded the Swiss researchers of patients with a condition known as antiphospholipid syndrome (APS). The rare condition, typically triggered by an infection, causes the body to develop antiphospholipid antibodies, which play an essential role in blood coagulation. What about the SARS-CoV-2 virus, they wondered.



A retrospective international cohort study was launched with 64 patients, divided into three groups: one with mild COVID-19 from the Principality of Liechtenstein and two cohorts with severe COVID-19 from Switzerland. Measurements included clinical parameters, laboratory inflammation markers and two distinctive aPL. Just as suspected, the researchers found a highly significant association with elevated IgA-aPL in patients with severe COVID-19. In addition, total IgA antibodies were significantly higher as well. LSI's tie in with the research extended beyond Hasan Ali's new fellowship in the **Penninger** Lab. Hasan Ali shared preliminary results with Dr. Penninger, seeking guidance on potential mechanisms of action and data interpretation. A subsequent study published in Clinical Infectious Diseases states the researchers saw a novel significant association of severe COVID-19 with IgA and IgA-aPL, that may emerge from a strong response against SARS-CoV-2 in the lung. [Read More.](#)
[Read the Paper.](#)

ANALYSIS CHALLENGES LONG-HELD ASSUMPTIONS ABOUT PATERNAL DNA METHYLATION IN THE FIRST STAGES OF LIFE



Julien Richard Albert finished his PhD in medical genetics on a crescendo, challenging the conventional wisdom on methylation of sperm DNA following fertilization of eggs. For years, sperm DNA has been thought to be mostly stripped of methylation (5-methylcytosine) in the aftermath of conception. But findings Richard Albert and colleagues published in [Nature Communications](#) showed that in the first stages of life, some regions on incoming paternal chromosomes actually show a robust increase in DNA methylation.

Not what Richard Albert expected, given the number of slides he'd seen presented by international experts that showed the wave of DNA methylation loss at this stage. He and mentor Dr. **Matthew Lorincz** already knew from previous microscopy experiments that the paternally inherited DNA is preferentially demethylated immediately following fertilization, while maternal DNA methylation levels remain relatively constant. The pair, in collaboration with colleagues at Tokyo University of Agriculture and colleagues at UBC employed high-resolution experiments to confirm that the paternally inherited DNA loses over 5 times more DNA methylation compared to maternal DNA.

While the vast majority of regions lost DNA methylation, as expected, a minority of regions showed antithetical yet robust gain of DNA methylation following fertilization. Working with colleagues at Japan's Kyushu University, the researchers identified maternally inherited DNMT3A proteins as being responsible for this new phenomenon. [Read More](#)

SHEDDING LIGHT ON IMPLICATIONS OF STAC3 MUTATIONS IN MUSCULAR DISORDERS

Five or more mutations in the STAC3 gene are known to influence muscular disorders, but little is known about how those mutations translate into the biochemistry of misfiring muscle contraction. PhD student **Britany Rufenach** and Dr. **Filip Van Petegem** are looking at how known mutations in the STAC3 gene affect excitation-contraction coupling. In a study published in [Structure](#), they analyzed the effect of the disease-associated variants, and their ability to bind to the calcium channel. With the aim of better understanding the molecular mechanisms of this disease, they looked specifically at how these mutations affect the binding of CaV1.1 (the calcium channel), because that interaction is vital for STAC3's role in muscle contraction.

STAC3 links two large membrane proteins in muscle cells: the voltage-gated calcium channel (CaV) located in the plasma membrane, and the Ryanodine receptor (RyR), located in the Sarcoplasmic reticulum. Its interaction with the CaV is understood, but how it couples with the RyR may reveal the mechanisms of many disease mutations. The researchers found that some of these are quite severe, knocking out the CaV completely, while others greatly weaken it. Other mutations act only to disrupt excitation contraction coupling, making a target for mutations causing myopathies and malignant hyperthermia. [Read More](#)

Image: Cover art for the August issue of *Structure* was created by Britany Rufenach, in her first outing with Blender, a 3-D modeling program. The image illustrates that when the link between the calcium channel (red) and STAC3 (blue) is broken, muscle function is impaired.



ACIDITY MAY PLAY A ROLE IN ESOPHAGEAL CANCER – AND POINT THE WAY TO NEW TREATMENT APPROACHES



Dr. **Shane Duggan** and an international team of researchers including UBC Dean of Medicine Dr. Dermot Kelleher have discovered that pH levels may play a key role in the metastasis of esophageal cancer as well as cellular changes that set the stage for its development. Their findings, reported in a cover story appearing in [Cellular and Molecular Gastroenterology and Hepatology](#) provide important context for precursor lesions, or wounds, that present in the esophagus, as well as the eventual escape or metastasis of cancer cells in esophageal adenocarcinoma (EAC).

The study showed that genes regulating differing forms of cellular movement and invasion used by esophageal cells during wound healing, precancerous cell expansion and metastatic processes are modulated by the surrounding pH levels. Only 14 per cent of Canadian patients remain alive five years after a diagnosis of esophageal cancer. Many patients who develop esophageal adenocarcinoma have a significant history of gastro-esophageal reflux disease, or GERD. Between 5-12 percent of Canadians have the condition, which causes pain, ulceration and inflammation. The episodic wounding of the tissues by stomach acid promotes the development and expansion of a genetically unstable, precancerous lesion known as Barrett's esophagus.

The researchers found novel functions for many genes in the regulation of both fast escape-like and slow invasive-type movements respectively. These may facilitate the expansion of Barrett's esophagus lesions, and metastasis of esophageal cancer cells. The pH environments encountered by esophageal cells may directly enable the niche for cancer development - and further progression that leads to such poor outcomes in esophageal cancer patients. Using high-content imaging analysis and screening, the team screened large, small interfering RNA (siRNA) libraries of 6,000 genes to identify those that impact cell shape and cell movement, leading to a fundamental insight about the relationship between cell shape and cancer metastasis. [Read More](#)

CIRCUMVENTING SELECTIVE PERMEABILITY: SMALL BINDING PROTEINS HITCH A RIDE INTO CELL CYTOSOL VIA SALMONELLA'S SENSORY PROBE



An international team led by LSI postdoctoral fellow **Antoine Chablotz** harnessed salmonella's syringe-like system to inject specific proteins into the fluid that fills cells.

More than a quarter of all human proteins are thought to bathe in this milieu, where they interact with one another as well as with proteins from every other cellular compartment. Yet until now, it's been impossible to efficiently study interactions between those proteins, as there was no system or means to enable other antibody-like proteins, such as DARPins and monobodies, to reach the cytosol. Both of these proteins can specifically inhibit certain protein-protein interactions that have significant therapeutic potential.

The team engineered a novel cytosolic protein delivery system enabling us to efficiently deliver those proteins directly inside the cell – once in the cytosol they can target essential protein-protein interactions with high specificity, a finding published online in [Communications Biology](#), a new, open-access journal produced by Nature. Piercing the wall surrounding eukaryotic cells has been done before, but the researchers did so for the first time with small binding proteins, namely DARPins and monobodies. In addition, they were able to specifically inhibit a protein called RAS, which is at the center of one of the most mutated pathways in cancer. [Read More](#)



Illustration: "Vienna science under the Salmonella sun," by Cian Karl Ebert, at the age of six.

PHD GRADUATE CHLOE GERAK TARGETS PROTEIN-PROTEIN INTERACTIONS AND TAKES AIM AT CANCER

Chloe Gerak took aim at the uncontrolled cell division in cancer using a combination of high-throughput screening, computational modeling, and NMR to find and characterize small molecule inhibitors of protein-protein interactions. In a study published in the [Journal of Biological Chemistry](#) her focus is on a member of the ETS family, ETV6, which plays an important role in embryonic development and hematopoietic regulation. Structurally, ETV6 has two protein domains: an ETS DNA-binding domain and a PNT domain. The PNT domain of ETV6 is of particular interest to Gerak, as it's able to self-polymerize, allowing for multiple PNT domains to come together, which then allows the ETS DNA-binding domain to bind to DNA with higher affinity.

The ETV6 PNT domain has been found in numerous chromosomal translocations, which have been found in over 40 different types of cancer. The cancer-causing mechanism is thought to be related to the PNT domain's self-polymerization property, as this brings the fusion proteins produced from the translocations together. If the fusion is to a receptor tyrosine kinase, this results in their dimerization, which is the mechanism that activates their kinase activity. This in turn stimulates downstream signaling pathways, often resulting in uncontrollable cell division and cancer. This makes the PNT domain a great target for a chemotherapy drug.

In her search for a molecule that will inhibit PNT domain polymerization, Gerak, a PhD candidate in the Department of Biochemistry and Molecular Biology at the Life Sciences Institute designed a high throughput split luciferase screening assay to do just that. After screening more than 17,000 compounds for a reduction in light (and therefore an inhibition in dimerization), she got a few hits, but they also resulted in the same decrease in emission in the control cell line. She screened an additional library that specifically targets protein-protein interactions. Working with a collaborator in Bristol, she used molecular modelling and their BUDE (Bristol University Docking Engine) virtual screening platform to screen 8.2 million compounds that were each in 20 different conformations to either interface of the PNT domains. The findings from these screens were published in [SLAS](#).

Dr. Gerak is now a postdoctoral fellow at the University of Melbourne in Australia. [Read more](#)



Photo by Paul H. Joseph/UBC Brand & Marketing

CONGRATULATIONS TO THIS YEAR'S LSI GRADUATES.

[See our LSI Graduate Gallery](#)

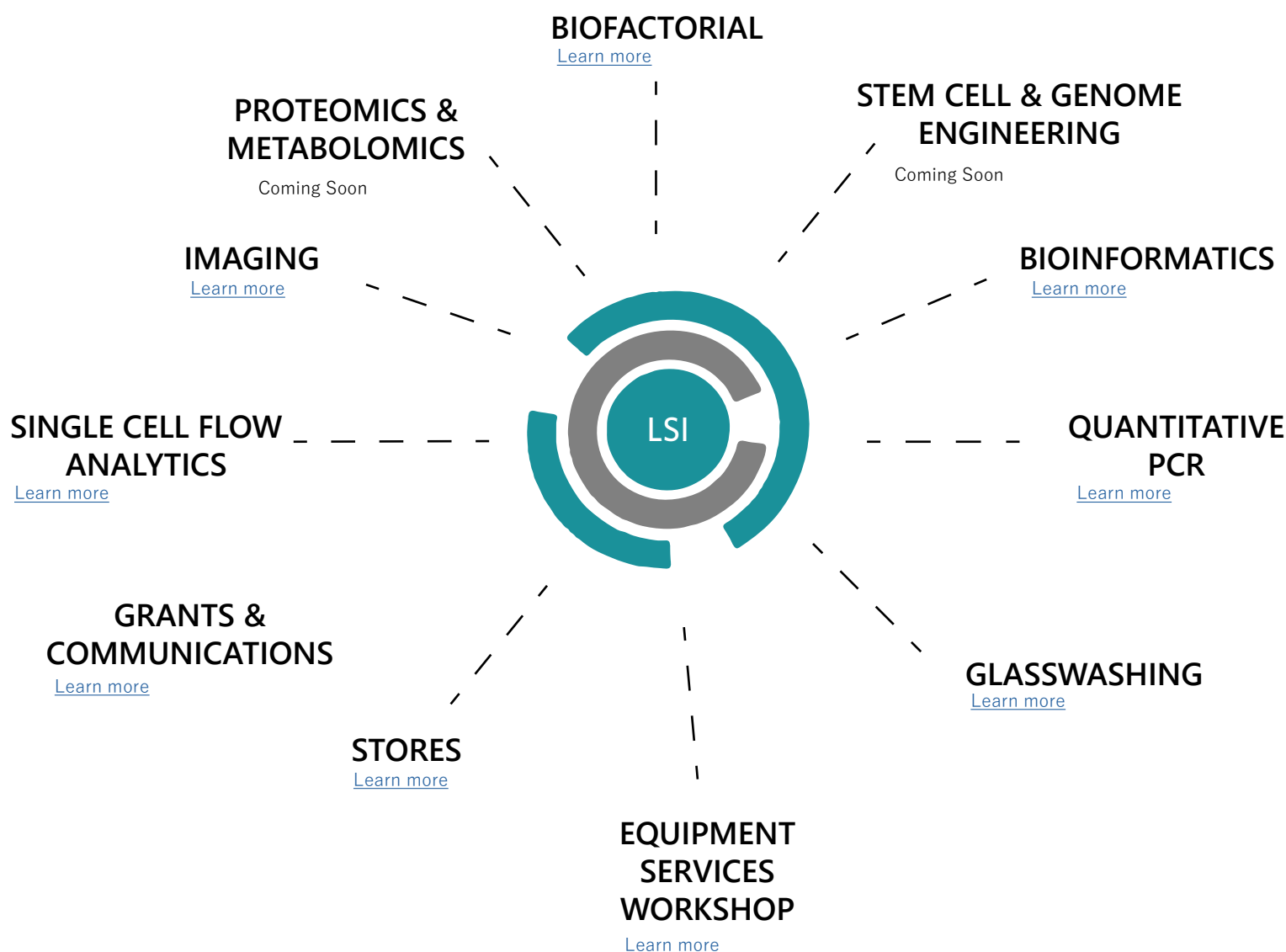


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To learn more about infrastructure available at the Life Sciences Institute and information about other facilities in the Life Sciences Centre, visit [our website](#).



ACKNOWLEDGEMENTS

The LSI is grateful to the Faculties of Medicine and Science as well as the offices of the Provost and VPRI, who have supported the institute tremendously over the past year, both financially and otherwise.

We would also like to acknowledge that during the 2020-2021 fiscal year, the LSI received substantial support from the federal government's Canada Research Continuity Emergency Fund, which helped support critical research infrastructure during the COVID-19 on-campus research curtailment period.

We would like to thank the following individuals for their assistance in the creation of this report: Bethany Becker, Richa Anand, Aryannah Rollinson, Nina Maeshima, and all LSI faculty, staff, and trainees.

APPENDIX

FULL LIST OF PUBLICATIONS

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