2025 Graduate Colloquium

April 28, 2025
Biology Building
Rooms 113, 121 & 122

Graduate Colloquium 2025 - Schedule

Biomedical Sciences - Room 121

Time	Format	Student	Supervisor
Session 1 - Chaired By: Dr. Munir Rahim			
9:00 am - 9:30 am			
	6 mins	Introduction & Welcome by Dr.Andrew Hubberstey	
	10 mins	Patel, Rachna	Dr. Phillip Karpowicz
	10 mins	Wnaiza, Jannatun	Dr. Phillip Karpowicz
9:30 am - 10:00 am			
	10 mins	Edwards, Christian	Dr. Phillip Karpowicz
	10 mins	Hinch, Isabelle	Dr. Lisa Porter
10:00 am - 10:30 am			
	10 mins	Alkassab, Mohamad	Dr. Munir Rahim
	10 mins	Eid, Ronaldo	Dr. Munir Rahim
10:30 am - 11:00 am - Coffee Break in Room 122			
Session 2 - Chaired By: Dr. Jeffery Dason			
11:00 am - 11:30 am			
	10 mins	Girgis, Sophia	Dr. Munir Rahim
	10 mins	Jassim, Maryam	Dr. John Hudson
11:30 am - 12:00 pm			
	10 mins	Badalova, Maria	Dr. Vijendra Sharma
	10 mins	Koboji, Rogers	Dr. Vijendra Sharma
12:00 pm - 12:30 pm			
	10 mins	St Louis, Alexandria	Dr. Jeffery Dason
	10 mins	Chot, Mathiang	Dr. Huiming Zhang
12:30 pm - 1:30 pm - Lunch and Poster Viewing in Room 122			
Session 3 - Chaired By: Dr. Dorota Lubanska			
1:30 pm - 2:15 pm			
	10 mins	Mahendran, Hema Priya	Dr. Lisa Porter
	10 mins	Ciesluskowski, Alan	Dr. Lisa Porter
	10 mins	Dinescu, Stephanie	Dr. Lisa Porter
2:15 pm - 2:45 pm			
	10 mins	Rahimi, Mahsa	Dr. Lisa Porter
	10 mins	Llancari, Amy	Dr. Lisa Porter
	10 mins	Martin, Jeffery	Dr. Lisa Porter
2:45 pm - 3:00 pm - Coffee Break in Room 122			
Session 4 - Chaired By: Dr. Brian Deveale			
3:00 pm - 3:30 pm			
	10 mins	Butt, Aqil	Dr. Brian Deveale
	10 mins	Nadi, Ali	Dr. Lisa Porter
	10 mins	Rajni	Dr. Andrew Swan
3:30 pm - 5:00 pm - Poster Viewing in Room 122 & Social in Biolearning Centre (BB223)			

Time-Restricted Feeding Effects on Colorectal Tumorigenesis in the Apc^{min} Model

Patel, R., V. Carmona-Alcocer, A. Mcbride, P. Karpowicz
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Karpowicz Lab, Biomedical Sciences

Circadian rhythms regulate daily physiology and impact cancer by regulating stress responses, anti-tumour immunity, metabolism, cell differentiation, apoptosis, and stem cell maintenance, including in the gastrointestinal tract. Many protein coding genes have circadian transcriptional rhythms regulated by the clock, and disruptions in clock activity can affect gastrointestinal regeneration. Previous work from my lab and others has shown that the loss of circadian rhythms via genetic or environmental clock disruption increases intestinal tumorigenesis via dysregulation of intestinal stem cell pathways.

Time-Restricted Feeding (TRF), where food availability is restricted to peak circadian activity, can boost and synchronize circadian rhythms and decrease tumour growth of lung cancer xenografts; however, whether TRF impacts the initiation of tumours is unknown. Apc^{min} mice develop tumours in the small intestine that are accelerated by circadian disruption. Pilot experiments performed in our lab suggest TRF reduces tumorigenesis in Apcmin mice; however, whether circadian rescue is involved is unknown.

To determine how TRF reduces tumourigenesis in Apc^{min} mice, I will perform TRF and analyze intestinal tissue. Intestinal tumour number and size will determine how TRF affects tumour initiation and growth, and histopathology will determine further changes in tumour and cell size, cell proliferation, apoptosis, translational activity, and other processes related to tumour growth, between TRF and non-TRF mice. Colon and liver RNA sequencing will reveal how TRF affects daily transcriptional rhythms over the entire circadian cycle. Together these tests will characterize the cell and molecular biology underlying the effects of TRF on intestinal tumorigenesis.

Modelling Circadian Disruption in Human Organoids

Wnaiza, J.[1], Karpowicz, P.[1]
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Circadian rhythms are internal 24-hour cycles regulating essential biological processes such as metabolism, cell proliferation, and immune response. These rhythms are maintained by a central clock in the hypothalamus that is synchronized with peripheral clocks in tissues like the liver, intestine, and colon. At the molecular level, the circadian clock operates through a transcription-translation feedback loop involving core clock genes: CLOCK, BMAL1, PER1-3, and CRY1-2. The CLOCK-BMAL1 heterodimer activates the transcription of PERs and CRYs, inhibiting CLOCK-BMAL1 activity, and forming a negative feedback loop. This cycle is tightly regulated by FBXL3, an E3 ubiquitin ligase, which targets CRY for degradation to consolidate rhythmicity. Recent lifestyle factors such as night shifts, irregular eating, and frequent time-zone travel can lead to circadian disruption and misalignment between central and peripheral clocks, contributing to chronic diseases, including colorectal cancer (CRC). In most CRC cases, APC is mutated, activating Wnt signalling, a key pathway involved in cell proliferation. Currently, there are no in vitro models to study human-specific circadian misalignment in a tissue-specific context. To address this gap, I will use human biopsy-derived intestinal organoids as a multicellular 3D model that mimics intestinal tissue architecture and has been shown to exhibit circadian rhythms. I will investigate whether organoids can autonomously maintain circadian oscillations using a BMAL1-luciferase reporter system. Using genetic knockout (KO) organoids of BMAL1, FBXL3, and APC, I will assess whether the disruption of these genes disrupts circadian clock transcription rhythms. My study will provide a novel platform to investigate clock-cancer interactions in human tissues.

Investigating the circadian clock in the intestinal stroma

Edwards, C, Phillip Karpowicz

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Karpowicz Lab, Biomedical Sciences

Circadian rhythms are patterns in biological activities entrained by light and food intake that align with the sleep and wake cycles of an organism. These rhythms allow our physiology and behaviour to anticipate changes in our environment over the 24-hour day. Circadian rhythms are controlled by a set of genes, BMAL1 and CLOCK, which heterodimerize and bind to regulatory sequences present on thousands of genes in our genome, providing timing in their transcription. Circadian rhythms are disrupted by common lifestyle factors such as jetlag, shift-work, and abnormal sleep cycles, leading to irregular physiological and behavioural responses in metabolism and regeneration. Advancements in society have led to constant food availability and increased exposure to artificial light, resulting in widespread presence of circadian disruption. This disruption is linked to the increasing prevalence of inflammatory bowel diseases in the gastrointestinal tract. The intestine is organized into crypts, where intestinal stem cells at the base drive rapid cellular turnover; PdgfRa+ telocytes near the crypt support stem cells by providing critical sources of factors like Wnt and Rspo1. Previous studies in my lab using mouse models of whole body and epithelial-specific Bmal1 KO have shown a worsening of colitis but the underlying mechanisms remain unclear, and indeed the circadian regulation of the intestinal stroma is unknown. I will examine how stromal-specific Bmal1 KO affects intestinal crypt architecture in PdgfRa-CreERT2; Bmal flox/flox mice. I predict that stromal clock loss will cause altered timing of stem secretions, resulting in altered morphology and regenerative potential.

The Role of Spy1 in Mammary Involution and Oncogenesis

Hinch, I., Fifiled, B., Porter L.A.

University of Windsor, Windsor, Ontario. N9B 3P4.

Porter Lab, Department of Integrative Biology/Biomedical Sciences

From puberty to menopause, factors attributed with breast cancer fluctuate with the natural mammary development. A period of increased breast cancer risk with increased metastasis and mortality occurs following childbirth – potentially linked to mammary involution: gland remodeling post lactation, which balances high rates of apoptosis and cell regeneration. Two processes controlled by the cell cycle and its regulators. The cyclin-like protein Spy1 can enable cell proliferation and override apoptosis. Spy1 levels have been found to be elevated breast cancer. Interestingly, levels of Spy1 are also elevated during involution. We hypothesized that Spy1 protects the cell population necessary for normal mammary gland reconstitution post involution. To address this, an in vitro mock involution model was deployed with the murine epithelial cell line (HC11) over a delivery and withdrawal of hormonal time course. This was paired with in vivo tissue collection of the mouse model overexpressing Spy1 in the mammary gland (MMTV-Spy1) over an involution time course. In vitro results suggest the ability of Spy1 of maintaining stemness post-differentiation, and in vivo data indicates failure of healthy epithelial clearing during involution. This research begins to articulate the role of Spy1 during normal mammary involution in maintaining the survival of epithelial cell populations, and how overexpression could potentially play a role in the predisposition of the breast to oncogenesis.

NKR-P1C receptor function in natural killer cells

Alkassab, M. [1], Rahim, M. [1]

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Rahim Lab, Biomedical Sciences

Natural killer (NK) cells are innate immune cells specialized in detection and elimination of diseased cells, such as cancer and virus-infected cells. They have cytotoxic function to kill diseased cells and produce cytokines, such as interferon-γ (IFN-γ), to modulate activity of other immune cells. NK cell functions are regulated by an array of activating and inhibitory receptors. NKR-P1C, the prototypic marker (NK1.1) for NK cells in C57BL/6 (B6) mice, is an activating type II transmembrane C-type lectin-like protein receptor encoded by Klrb1c gene. NKR-P1C is one of the earliest receptors expressed in developing NK cells, but no endogenous ligand for this receptor has been identified. More recently, m12 protein from murine cytomegalovirus (MCMV) was shown to bind NKR-P1C, suggesting a role for this receptor in immunity against MCMV infection. We have generated Klrb1c$^{-/-}$ mice, which lack NKR-P1C expression, to investigate its functions in NK cells. NK cell development and distribution is unaffected in the lymphoid tissues from Klrb1c$^{-/-}$ mice. NKR-P1C-deficient NK cells express key activating and inhibitory receptors and remain functionally competent in vitro—except for NKR-P1C–mediated responses. Following MCMV infection, Klrb1c$^{-/-}$ mice exhibited significantly reduced NK cell proliferation compared to wild-type (WT) control mice. Ongoing work aims to establish the role of NKR-P1C in mediating immunity against MCMV infection by identifying viral m12 protein in infected cells. These findings will provide new insights into the role of NKR-P1C in NK cell biology and antiviral immunity during MCMV infection in mice.

Exploring NKR-P1C receptor function in type 1 innate lymphoid cells

Eid, R.[1], Rahim, M.M.A.

Rahim Lab, Biomedical Sciences

Tissue-resident type 1 innate lymphoid cells (ILC1s) are a subset of immune cells that produce type I cytokines, including IFNγ and TNFα, to limit pathogen replication during the earliest stages of infection. As such, ILC1s play an indispensable role in host immunity, and their ablation impairs immunity against murine cytomegalovirus (MCMV) in mice. While ILC1s have an overlapping receptor repertoire with the more cytotoxic ILC subset, the natural killer (NK) cells; the role of some of these receptors in ILC1 biology is not known. Of particular interest is the activating NKR-P1C receptor, encoded by the *Klrb1c* gene, which is expressed in NK cells and ILC1s. NKR-P1C is a type II transmembrane protein with an extracellular C-type lectin-like domain that is associated with an intracellular adaptor protein to drive cell activation upon ligand binding. The endogenous ligand for NKR-P1C is unknown, but it was shown to bind to a viral ligand, MCMV m12 protein. We hypothesize that NKR-P1C is a positive regulator of ILC1 functions. Using *Klrb1c*$^{-/-}$ mice, we will study NKR-P1C function in ILC1 and its role in immunity against MCMV infection. To determine NKR-P1C function in ILC1s, we will analyze ILC1 phenotype, development, maturation, distribution, and function across different tissues in wild-type (WT) and *Klrb1c*$^{-/-}$ mice. To determine the role of NKR-P1C in ILC1-mediated antiviral responses, we will analyze ILC1 activity and its contribution in controlling MCMV infection in WT and *Klrb1c*$^{-/-}$ mice. This study will reveal the function of an orphan NKR-P1C receptor in ILC1 biology.

Session 1 – Voting

The Effects of IL-23 on NK Cell-Mediated Tumor Surveillance and Dysfunction

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Rahim Lab, Biomedical Sciences

Natural Killer (NK) cells are a type of lymphocytes that are a part of the innate immune system. NK cells have the capacity to kill diseased cells, including tumor cells, virally infected cells, intracellular pathogens, and stressed cells. NK cells respond to target cells via functions mediated by the overall signaling balance of their activating and inhibitory receptors. NK cells become dysfunctional in solid tumors, but the mechanisms are not fully understood. NK cell responses are modulated by cytokines in the tumor microenvironment. IL-23 and IL-12 are cytokines that share a common receptor (IL-12-Rβ1) subunit and are thought to have opposite effects on NK cell functions. IL-12 is known to boost NK cell activity and foster anti-tumor responses, but IL-23's role is more nuanced, with evidence indicating that it can inhibit NK cells. The work in our lab has shown NK cell dysfunction and high levels of IL-23 in the mouse mammary tumors. We hypothesize that IL-23 in tumors induce NK cell dysfunction. My preliminary experiments detected high levels of IL-23 receptor (IL23R) expression in tumor-infiltrating NK cells compared to splenic NK cells, as well as decreased cytokine production and degranulation when NK cells were treated with IL-23 in vitro. Future analyses will determine how IL-23 induces NK cell dysfunction, and whether blocking IL-23 can enhance NK cell responses in tumors. This study is expected to reveal a possible mechanism by which NK cells lose activity in solid tumors, and a potential target for cancer therapy.

Characterization of the Effect of Camelid WNT16B Antibody Treatment on Mammalian Cancer Cell Lines

Jassim, M. [1] , Hudson, J. W.[2]

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Hudson Lab, Biomedical Sciences

Chemoresistance remains a significant barrier to effective cancer treatments and is closely associated with cancer recurrence. One protein that plays a role in this process is WNT16B, which becomes overexpressed in response to DNA damage within the tumor microenvironment. This in turn activates the WNT/β-Catenin signaling pathway. This activation promotes tumor cell survival and proliferation (Sun Y et al., 2012; Zhan T et al., 2017). In this study, we aim to evaluate the therapeutic potential of anti-WNT16B camelid IgG antibodies as a means to suppress downstream oncogenic targets of the WNT/β-Catenin pathway and to reduce cancer cell viability.

The focus of our research is to determine whether treating cancer cell lines with Camelid WNT16B antibodies will affect cancer cell proliferation and downstream targets of the WNT//β-Catenin signaling pathway in liver cancer (HepG2), cervical cancer (HeLa), and breast cancer (MCF-7) cell lines. We have established WNT16B levels in the aforementioned cell lines by western blot analysis. We will assess whether the antibody can effectively bind and neutralize the effects of WNT16B, leading to a change in WNT/β-Catenin signaling and alterations in cell proliferation and apoptosis. Following antibody treatment, cell viability and apoptosis will be evaluated using Trypan Blue exclusion and annexin V assays.

We have also analyzed β-Catenin and c-Myc levels after treatment with camelid WNT16B IgG1 via western blot. We will be performing more analyses on additional downstream targets of the WNT/β-Catenin pathway involved in cancer cell proliferation and cancer recurrence, such as Cyclin D1, Axin2, Survivin, and MMP7.

While this project is limited to in vitro analysis, future directions include in vivo studies to further assess the antibody's ability to overcome chemoresistance and enhance therapeutic outcomes in cancer models.

Identification of cell-type-specific mRNA translational control mechanisms in synaptic plasticity and memory formation

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Sharma Lab, Biomedical Science

The formation of long-term memories in the brain relies on the synthesis of new proteins through mRNA translation. The two primary types of long-lasting synaptic plasticity are long-term potentiation (LTP) and long-term depression (LTD). LTP is characterized by a sustained increase in synaptic strength, while LTD involves a decrease in synaptic strength. Both processes are essential for information storage, learning, and memory, with LTD being particularly important for spatial and object recognition memory. The activation of the eukaryotic initiation factor 2 (eIF2) pathway is crucial for LTD, followed by the synthesis of new proteins. Four specific kinases in the brain regulate the phosphorylation of eIF2α (p-eIF2α), and research shows that this is vital for learning behaviour. However, the distinct cellular and molecular mechanisms through which p-eIF2α-dependent translation promotes LTD in various cell types remain largely uncharacterized. We hypothesize that learning activates specific kinases that phosphorylate eIF2α, promoting the production of proteins critical for LTD in specific cell types involved in memory. This study aims to investigate the mechanisms that neurons and glial cells use to coordinate protein synthesis processes essential for memory. To test this hypothesis, mice will undergo spatial and object recognition tasks, which induce LTD. We will use immunohistochemistry to assess levels of phosphorylated eIF2α in different cell types. Understanding the roles of these cell types in p-eIF2α-mediated translation can deepen our knowledge of how the brain encodes and stores long-term memories, with potential implications for treating memory-related disorders.

Cell-type-specific Role of eIF2α Pathway in Aged and Alzheimer's disease Brain

Koboji, R., Badalova, M., Reeves, M., Sharma, V.

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Sharma Lab, Biomedical Sciences

mRNA translation in the brain is crucial for consolidating long-term memories, and its dysregulation is linked to memory loss associated with aging and Alzheimer's disease (AD). Aging is the most significant risk factor for AD, with individuals aged 65 and older at a heightened risk. Key pathological features of Alzheimer's disease include the buildup of amyloid-beta peptides and hyperphosphorylated tau proteins. This accumulation triggers various stressors that activate the integrated stress response, which leads to the phosphorylation of the α subunit of eukaryotic initiation factor 2 (p-eIF2α) and inhibits general protein synthesis. Prolonged activation of this stress response in Alzheimer's disease elevates p-eIF2α levels, reduces overall protein synthesis, and negatively impacts long-term memory consolidation. p-eIF2α plays a vital role in translational control, influencing memory processes in both healthy and diseased states. In a healthy brain, learning fosters protein synthesis through the dephosphorylation of p-eIF2α. However, the specific mechanisms regulating translation in different cell types during aging and Alzheimer's disease are still unclear. It is hypothesized that inhibited protein synthesis in AD and aging arises from cell-type-specific stress and elevated p-eIF2α levels, which disrupt essential cellular functions for synaptic plasticity and memory formation. To explore this, behavioral, genetic, and pharmacological techniques will be employed to assess memory deficits in aged and AD mice and identify brain cell types under cellular stress. Understanding these mechanisms could lead to targeted therapeutics, improving treatment outcomes for Alzheimer's disease and related memory disorders.

Loss of Calcium Binding Protein Frequenin Results in Nociceptive Hypersensitivity in *Drosophila melanogaster*

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Chronic pain is difficult to treat due to a lack of understanding of its molecular components and mechanisms; however, one potential driving factor is changes in neuronal excitability due to calcium dysregulation. Interestingly, through a screen of well-known Drosophila calcium binding proteins, we determined only loss of Frequenin (Frq-1, Frq-2) resulted in nociceptive hypersensitivity. Neuronal Calcium Sensor-1, the human orthologue of Drosophila calcium binding proteins Frequenin-1 and Frequenin-2, has been suggested in vitro to be associated with nociceptive sensitization through changes in intracellular calcium. We hypothesize that Frq is required for standard nociception, potentially through both structural and functional mechanisms. Firstly, we used CRISPR-Cas9 to tag the endogenous *frq1* and *frq2* genes with a flag epitope. We found that Frq1 and Frq2 are widely expressed in the *Drosophila* central nervous system, and this localization overlaps with the nociceptive circuit. Although behavioural sensitization seen in loss of Frq also correlated with an increase in dendritic branching, current experiments are exploring physiological mechanisms through changes in calcium in the nociceptive circuit upon the loss of Frq. Collectively, our data demonstrates a unique and novel role for Frq1 and Frq2 in nociception.

Processing of two competing sounds in the rat's auditory midbrain neurons depends on temporal differences

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Zhang Lab, Biomedical Sciences

A natural acoustic environment consists of competing sounds of different qualities that reach the two ears either simultaneously or at different times. The ability to segregate and streamline acoustic information carried by different sounds and form coherent acoustic images of individual sounds is essential for animal (including human) behaviours. Psychoacoustical and neurophysiological experiments have been conducted to study neural processing of acoustic information in a natural acoustic environment. However, mechanisms underlying such processing are still poorly understood. In this study, we examined the neural processing of two competing tone bursts with different frequencies in the rat's inferior colliculus, a major auditory integration centre in the midbrain. Neural responses were elicited by a pair of leading-trailing tone bursts with various temporal gaps. We recorded action potentials from 24 well-isolated single neurons and studied how the strength and timing of responses were dependent on the time gap between the two sounds. Results suggested that the response to a leading sound was not affected by a trailing sound. However, the strength of response to the trailing sound was reduced while the latency of the onset time of response was lengthened and became more variable when the time gap between the two sounds was reduced. Interestingly, the response to the trailing sound wasn't completely abolished even when a trailing sound immediately followed a leading sound, suggesting that neurons could detect a small frequency difference between the two-tone bursts. These findings provide new insights into neural processing of competing sounds in an acoustic environment.

Session 2 – Voting

SPY1-Mediated Cell Cycle Regulation as a Target to Overcome GSC-induced Therapy Resistance in Glioblastoma

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Glioblastoma (GBM) is an extremely lethal type of a brain tumour evading all intricate attempts of modern therapies. Extensive genetic analyses of GBM have indicated a variety of deregulated molecular pathways involved in DNA repair, apoptosis, cell migration\adhesion and cell cycle regulation. Brain tumor initiating cells (BTICs) aid in the initiation, progression, and therapy resistance of heterogenous mass of glioblastoma and are responsible for post-therapy tumour recurrence. BTICs share properties with normal neural stem cells (NSCs), including ability to self-renew and giving rise to differentiated progeny. Previously, our lab established that the levels of an atypical cell cycle protein, SPY1 (RINGO; gene SPDYA) are elevated in malignant human glioma and its upregulation correlates with poor prognosis of patients with GBM. SPY1 is responsible for the symmetric division of BTICs in subsets of high-grade glioma leading to aberrant expansion of those aggressive populations of cells. Spy1 activates Cyclin Dependent Kinases (CDK) and has been demonstrated to override protective cell cycle checkpoints. We hypothesize that select targeting of SPY1-CDKs will be an effective therapeutic intervention for subsets of GBM patients. My research project focuses on how targeting of SPY1 can contribute to better control over the growth and progression of GBM by eliminating BTIC populations. The objectives of my study will allow for evaluation of GBM biology in face of SPY1 depletion and functional assessment utilizing GBM patient-derived, three-dimensional spheroids and *in vivo* zebrafish Patient Derived Xenograft (PDX) screening platform.

Exploring principles of the interplay between tumour initiating cells and the endothelial component in glioblastoma

Cieslukowski, A.[1], Lubanska, D.[1], Fidalgo da Silva, E.[1], Soliman, M.A.R.[2,3], Shamisa, A.[4], deCarvalho, A.[5], Kulkarni, S.[4], Porter, L.A.[1]

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Porter Lab, Biomedical Sciences

Efficient targeting of multiple components of a tumour might be a successful strategy in aggressive types of cancer such as glioblastoma (GBM), which for decades now remains the most common and malignant primary brain tumour with an extremely poor patient survival of less than 15 months. The significant therapeutic challenge posed by GBM stems from its genetic and phenotypic heterogeneity fueled by multiple components of the tumour biology including aggressive, treatment-resistant populations of Tumour Initiating Cells (TICs), as well as high levels of angiogenesis contributing to tumour evolution. TICs, which are at the source of GBM patient relapse, thrive in niches adjacent to blood vessels where they interact with endothelial cells (ECs) to evade therapies. TICs can be identified by the presence of two well-established cell surface markers- CD133 and CD44. Targeted antiangiogenic drugs, which prevent the recruitment of ECs by GBM tumour cells, are effective in only 50% of patients and offer temporary benefit due to acquired secondary resistance. Thus, there is an urgent need for novel, effective therapeutic strategies. This project investigates the impact of ECs on the aggressive characteristics of individual, specific populations of TICs using GBM patient-derived systems, including three-dimensional organoid models and zebrafish patient-derived xenografts (zPDXs). Secreted factors from ECs seem to expand the CD44+ TIC population through preferential selection or evolution of other TIC populations. Subsequently, this appears to contribute to enhanced therapy resistance. Elucidating the details of this TIC-EC interplay could lead to the identification of novel molecular targets against treatment-resistant TICs.

The Role of Spy1 in Overriding Senescence in Glioblastoma (GBM)

Dinescu, S., Lubanska, D., Porter, L.A.

Porter Lab, Biomedical Sciences

Glioblastoma (GBM) is a highly aggressive malignant brain tumour with a poor prognosis despite intensive conventional therapies. A key challenge in treating GBM is its ability to resist treatment, with a subset of tumour cells surviving and entering cellular senescence, a state of irreversible cell cycle arrest. While senescence initially halts tumour growth, prolonged senescence can contribute to tumor recurrence. Spy1, a cyclin-like protein, is elevated in GBM and promotes cell cycle progression by activating cyclin-dependent kinases (CDKs) and overriding cell cycle checkpoints. We hypothesize that Spy1 promotes GBM tumour growth and progression by enabling cancerous cells to evade senescence. Using in vitro and ex-vivo systems, this project will explore Spy1's influence on senescence in GBM and assesses whether Spy1 targeting can enhance the effect of therapies targeting senescent cells. Spy1 will first be knocked down in GBM cell lines, and the levels of senescence will be evaluated through senescence-associated β-galactosidase staining and transcriptional analysis of senescence markers. These assessments will be replicated in Spy1-knockdown GBM cell lines subjected to temozolomide, the conventional treatment for GBM. Furthermore, this project will explore the combination of Spy1 inhibition with senolytic drugs, which are designed to eliminate senescent cells. The therapeutic efficacy of this combination will be evaluated through cell viability assays to assess cell death. This research will contribute to the understanding of Spy1's role in GBM and its potential as a novel therapeutic target, potentially paving the way for personalized therapies to prevent GBM progression.

Comparison of hepatic gene expression profiles between cirrhotic and non-cirrhotic HCC

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Hepatocellular carcinoma (HCC) ranks among the leading causes of cancer-related deaths globally. Metabolic Associated Steatotic Liver Disease (MASLD), the most prevalent liver condition, is closely linked to a spectrum of hepatic disorders, including Metabolic Associated Steatohepatitis (MASH), liver cirrhosis, and eventually HCC. While cirrhosis is a well-established precursor to HCC, approximately 20% of HCC cases arise without prior cirrhosis, and the molecular mechanisms driving this subset of non-cirrhotic HCC remain poorly understood. It is of utmost importance to understand the differences driving disease progression in cirrhotic versus non-cirrhotic HCC.

This study analyzed mRNA expression datasets to identify differentially expressed genes (DEGs) in MASLD/MASH and both cirrhotic and non-cirrhotic HCC compared to normal liver tissue. GO analysis revealed involvement of DEGs in lipid metabolism, cell proliferation, adhesion, migration, and immune response pathways. Core genes involved in cell cycle regulation were identified and compared across disease stages. For In vitro assays, we used our panel of HCC cell lines to test the effects of manipulation of Spy1 and/or Cdk inhibition. Zebrafish xenograft model used for in vivo assessment of Spy1 and CKIs. This work may identify Spy1 as a prognostic indicator and/or a potential therapeutic target for liver diseases such as HCC.

This comprehensive bioinformatics analysis identified core genes that mediate the molecular mechanisms underlying MASLD and MASH and their potential roles in non-cirrhotic HCC development. These findings provide a deeper understanding of the molecular basis of non-cirrhotic HCC and establish Spy1 as a prognostic marker and potential therapeutic target in liver disease and HCC.

The Role of Biological Sex on the Progression of Metabolic Dysfunction-associated Steatotic Liver Disease

Llancari, A. E[1], Fifield, B.[1], Jimenez-Ramos, M.[2], Kendall, T.J.[2], Fallowfield[2], J.A., Porter, L.A.[1,2]

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Porter Lab, Biomedical Sciences

Metabolic dysfunction-associated steatotic liver disease (MASLD) is an emerging global health concern, affecting nearly one-third of the population and rising in prevalence. As a sexually dimorphic organ, the liver exhibits sex-specific differences in MASLD, with men showing a higher prevalence than women, particularly before menopause. However, the mechanisms underlying sex-specific differences in disease progression remain poorly defined.

This study aimed to investigate sex-specific responses to MASLD using both experimental and bioinformatic approaches. First, a murine model was employed in which male and female mice were fed a methionine-choline deficient (MCD) diet to induce MASLD. Liver tissue was analyzed to assess morphological and cellular responses to injury. Second, through a collaboration with the University of Edinburgh, we leveraged SteatoSITE, the world's first data commons for MASLD. This unique multimodal resource integrates histopathological, transcriptomic, and electronic health record data, including patient demographics, and medication history. Using RStudio, patients were stratified by biological sex and disease stage for subsequent bioinformatic analyses, including differential gene expression and gene set enrichment analyses.

Our findings revealed marked sex-specific differences in liver injury and morphology in murine models. In human datasets, we identified distinct patterns of gene regulation and pathway enrichment between males and females. These results underscore the importance of considering sex as a biological variable in MASLD research. By combining experimental and computational methods, this study provides novel insights into sex-specific disease mechanisms, highlighting potential biomarkers and therapeutic targets to support precision medicine in MASLD.

A Novel Platform to Monitor and Prevent Prostate Cancer Progression

Martin, J., Fidalgo Da Silva, E., Porter, L.

Porter Lab, Biomedical Sciences

Prostate cancer (PC) is the second most common cancer in men worldwide, affecting 76 men daily in Canada. As treatment options continue to evolve, disease management and overall patient outcomes have improved. While effective, these treatments can sometimes pressure PC cells to transdifferentiate into a more aggressive, treatment resistant type of PC, known as neuroendocrine prostate cancer (NEPC). Treatment options for NEPC are limited as it is resistant to all current therapies, leading to a poor overall prognosis with an estimated survival of less than one year. Furthermore, the PC to NEPC transdifferentiation mechanism is not well understood, with few markers being used to study progression. Our lab has identified a class of cell cycle regulatory proteins elevated in NEPC, with evidence supporting that these proteins have the potential to drive progression to this drug-resistant form of disease. This project aims to establish a PC to NEPC platform of disease progression to study the specific role of these regulatory proteins during PC transdifferentiation. Further, we will utilize drugs that can inhibit these proteins and test whether these drugs can treat and/or prevent the progression of disease to NEPC. This work will be completed using in vitro and in vivo models, including human samples. Preventing the progression of disease to NEPC and identifying markers of NEPC remains one of the greatest challenges in this field, and we have strong rationale and data to support this being a promising direction that could make a meaningful impact for PC patients.

Session 3 – Voting

Uncovering miR-142 Targets Regulating B-cell Expansion in Non-Hodgkin's Lymphoma

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Non-Hodgkin's Lymphoma (NHL) is the fifth most prevalent type of cancer in Canada. Diffuse Large B-cell Lymphoma (DLBCL) accounts for 90% of aggressive NHL cases. The microRNA miR-142 is mutated in 20% of DLBCL cases. Additionally, miR-142 -/- B-cells display increased expansion and elevated B-cell Activating Factor Receptor (BAFF-R) expression. However, it remains unclear whether loss of miR-142 directly leads to elevated BAFF-R expression, leading to increased expansion. Mutating the miR-142 target site on BAFF-R and expanding B-cells could help elucidate the regulatory mechanism. If miR-142 target site KO B-cells expand more, it shows that miR-142 directly regulates BAFF-R expression. The miR-142 target site will be deleted using CRISPR. A gRNA targeting the miR-142 binding site on BAFF-R will be cloned into the PX458 plasmid, which contains the cas9 expression cassette. The resulting plasmid will then be transfected into B-cells. The transfected B-cells will then be cultured in vitro under conditions that promote B-cell expansion. The frequency of miR-142 target site mutations will be quantified via sequencing before and after expansion. If mutations are enriched in the expanded population, it would suggest that miR-142 directly regulates BAFF-R. Thus, in miR-142 -/- mice, the lack of regulation by miR-142 would be directly leading to increased levels of BAFF-R, driving increased B-cell expansion. A broader screen targeting all miR-142 targets could help uncover other critical regulators of B-cell expansion. These targets could then be studied further to develop therapeutic strategies for treating DLBCL, given that microRNAs are difficult to mimic therapeutically.

Tuberin as a Tumor Suppressor and Molecular Integrator of Growth Signaling and Cell Cycle Control

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The controlled growth and proliferation of a cell depend on its ability to sense both internal and external conditions and mount appropriate physiological responses. When such regulations go awry, various proliferative diseases may arise, including but not limited to cancers. Central to this control is the cell cycle, a precisely coordinated process that integrates metabolic signals, environmental conditions, and stress responses to maintain cellular homeostasis and ensure proper cell division.

The tumour suppressor Tuberin (*TSC2*) is a key regulator of the cell cycle, yet its role in directly controlling cell proliferation remains poorly understood. Our lab has demonstrated that mitogen and nutrient signaling cascades converge on Tuberin to regulate its interaction with the mitotic cyclin, Cyclin B1 (*CCNB1*), thereby modulating mitotic entry in a context-dependent manner. Using in vitro ectopic expression and CRISPR/Cas-based approaches, coupled with imaging and cell cycle analysis, we show that weakening Tuberin's interaction with Cyclin B1—either by altering its phosphorylation status or introducing loss-of-function TSC2 mutations—accelerates mitotic entry, increases proliferation, and leads to aberrant cellular phenotypes.

By characterizing Tuberin as a non-canonical regulator of mitotic entry, this research provides new insights into how metabolic signaling influences cell cycle progression. Given the frequent dysregulation of *TSC2* in cancer and other proliferative disorders, elucidating this mechanism could reveal novel therapeutic targets for controlling aberrant cell division in disease.

The Role of Anaphase Promoting Complex in Drosophila Female Meiosis

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In eukaryotes, the Anaphase-Promoting Complex/Cyclosome (APC/C) is a multi-subunit ubiquitin ligase that regulates cell cycle progression by targeting specific proteins for degradation. Its mitotic activity depends on co-activators Fizzy (Fzy/Cdc20) and Fizzy-related (Fzr/Cdh1). Although APC/C also functions in meiosis, its role there is less defined. *Drosophila melanogaster* serves as an excellent model to study meiotic regulation, particularly in oocytes, which initially arrest at prophase I. Meiotic resumption occurs during oocyte maturation, followed by a second arrest at metaphase I. APC/C is critical for proper meiotic progression and completion in female *Drosophila*. Its activation depends on phosphorylation of specific subunits. Cyclin B3 (CycB3), together with Cyclin-Dependent Kinase 1 (Cdk1), has been implicated in this activation. In female meiosis across several animal species, CycB3-Cdk1 facilitates anaphase onset. One of the three minimal CDK phosphorylation sites in the APC3 subunit is specifically regulated by CycB3-Cdk1 and is essential for APC/C activation. To investigate this mechanism, we propose a rescue experiment using a phosphorylated mutant of APC3. Additionally, Rca1, the *Drosophila* homolog of vertebrate Emi1/Emi2, acts as an inhibitor of APC/C-Fzr. To assess its role, we will use gal4-mediated RNA interference (RNAi) to knock down Rca1 and evaluate the resulting meiotic phenotype. Recent advances in mutant and knockdown analysis in *Drosophila* oogenesis offer powerful tools to unravel the coordinated action of cell cycle regulators during meiosis.

Session 4 – Voting