Abstract Booklet

2026 I3V Student Research Day

Infection, Immunity, Inflammation & Vaccinology (I3V)

Keynote Speaker:

Dr. Judith Mandl, PhD

Associate Professor, McGill University

Tuesday, May 26, 2026, CHEB Room 170, Halifax, NS

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Keynote Speaker: Dr. Judith Mandl, PhD

The emerging role of T cell proprioception in cell fate and immunity

Judith Mandl, PhD, is a former Canada Research Chair in Immune Cell Dynamics, and Associate Professor in the Department of Physiology, an associate member of the Department of Microbiology and Immunology, and of the Goodman Cancer Center at McGill University. She began her career as a computational biologist focused on the ecology and evolution of infectious diseases. Bringing her modeling expertise to within-host viral dynamics, she did her PhD at Emory University in the Population Biology, Ecology, and Evolution program in the lab of Dr. Mark Feinberg, studying the pathogenesis of Human and Simian Immunodeficiency viruses. She then completed a postdoc at the NIAID, NIH, with Dr. Ronald Germain in the Systems Biology group, where she investigated T cell trafficking dynamics.

Currently, Dr. Mandl's research focuses on investigating (1) immunodeficiencies that arise from defects in cell migration and impair T cell immunity; (2) specific challenges for immune cell motility in tissues, such as cellular crowding and mechanical forces; and (3) the architecture of the T cell receptor repertoire and the importance of sub-threshold T cell receptor interactions with self-peptide MHC in lymphoid organs in determining T cell effector potential. She is also fascinated by, and has written about, immune responses to viruses in their reservoir hosts, such as primates and bats. Mandl's team takes a highly multi-disciplinary, quantitative, and systems-driven approach, implementing state-of-the-art microscopy, sequencing, and quantitative analysis tools to link individual cell behavior with cell-population and organismal-level outcomes.

Role of taurine metabolism in inflammation and gut-brain communication in *Drosophila melanogaster*

Ahsan Malick [1]

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Neurodegenerative diseases (NDs) are conditions that cause strain to both healthcare and quality of life. Despite their burden, the aetiologies of NDs are poorly understood. Recent evidence points to changes in gut metabolism as an early mechanism influencing gut-brain communication and eventually onset of NDs. Under metabolic perturbed conditions, certain metabolites/nutrients could be endogenously upregulated or exogenously ingested to manage damage associated with metabolic deficiency. One such metabolite is taurine, an amino sulfonic acid with essential physiological and signaling functions. Previous lab work on *Drosophila melanogaster* (fruit fly) found that better aging flies with no ND symptoms produce higher taurine in the guts. Thus, I hypothesized that taurine would be a neuroprotective factor in the gut-brain axis that, when depleted, leads to ND-like symptoms. To test this hypothesis, I utilized the UAS-Gal4 system to create transgenic *Drosophila melanogaster* flies expressing small-interfering RNA sequences to knockdown peroxisomes, which are key metabolic organelles, as well as taurine synthesis enzymes through RNA-mediated interference. I utilized the negative geotaxis climbing assays (NGCA) to test for locomotor ability in wild-type and mutant flies treated with either taurine-supplemented food or a regular cornmeal diet (CMD). Results showed that flies climbed better over aging on a taurine diet compared to a CMD diet. Moreover, I performed immunofluorescence experiments on the guts of control and mutant flies fed with and without taurine, which indicated that taurine supplementation had noticeable changes on gut morphology. Finally, I looked at expression of neuropeptide signals in the different conditions, indicating taurine was affecting expression of known neuroinflammatory signals. Overall, my study in the fruit fly, a validated model to study neurodegeneration and inter-organ communication, helps identify conserved mechanisms that will help to define the onset of sporadic NDs in humans.

Targeting LINC01929 upregulates immunoproteasome activity through interferon I signaling in breast cancer

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Introduction:
Breast cancer is a leading cause of cancer-related deaths in women. Despite advances in immunotherapies, breast cancers are often resistant to these treatments due to inefficient antigen presentation, often caused by downregulated immunoproteasomes. We have identified long non-coding RNA LINC01929 is overexpressed in breast cancer tissues and associated with worse patient survival, reduced T cell tumor infiltration, and gene expression changes associated with dysregulated antigen presentation. To investigate the underlying mechanism, our study focuses on deciphering the effect of LINC01929 on type I interferon (IFN) signaling and immunoproteasome activity.

Methods:
MCF7 and MDA-MB-231 breast cancer cell lines are treated with antisense oligonucleotides (ASO) to reduce LINC01929 levels and then used in the following assays: qPCR for antigen presentation-associated genes, western blots of immunoproteasome- and type I IFN-associated proteins, and fluorogenic substrate assays to assess immunoproteasome activity. We use Anifrolumab, a monoclonal antibody that blocks type I IFN signaling, in combination with the ASO to confirm LINC01929 mediates antigen presentation through type I IFN signaling.

Results:
Targeting LINC01929 upregulates the expression of key immunoproteasome subunits, including proteasome subunit beta type-8 (PSMB8), and increases overall immunoproteasome activity. This coincides with upregulation of STAT1 and its phosphorylated forms at tyrosine-701 and serine-727. Anifrolumab treatment blocks all these effects induced by LINC01920 knockdown in the breast cancer cells.

Conclusions:
LINC01929 suppresses antigen presentation and induces a cold breast tumor microenvironment through suppressing type I IFN signaling. Targeting LINC01929 may be a novel therapeutic avenue to overcome breast cancer resistance to immunotherapy.

A Conserved G-Loop Motif in Tir Mediates ATP Binding and Contributes to EPEC Virulence

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Enteropathogenic and Enterohemorrhagic Escherichia coli (EPEC/EHEC, respectively) are major causes of diarrheal disease and rely on a type III secretion system (T3SS) to inject multiple effector proteins into host cells during infection. Host colonization requires EPEC to phosphorylate its CesT chaperone. Furthermore, an EPEC translocated intimin receptor (the Tir effector) mediates intimate attachment to intestinal cells. The molecular mechanisms controlling this process remain undefined, including how CesT phosphorylation occurs and what bacterial kinase is involved.

To that end, we searched the EPEC virulence-associated proteome for proteins with potential ATP-binding sites. We identified that the Tir effector contains a strictly conserved glycine-rich (GxGxxG) 'G-loop' motif that is known to mediate ATP-binding in eukaryotic protein kinases (e.g., Protein Kinase A). We therefore asked whether the Tir G-loop functions as a bona fide ATP-binding motif, and whether the Tir G-loop is required for EPEC virulence.

To experimentally address this, we investigated Tir G-loop ATP-binding capacity using an in vitro ATP-binding assay and explored its role in EPEC infection. Using a fluorescent ATP analog (TNP-ATP), we demonstrate that recombinant Tir binds TNP-ATP in a G-loop-dependent manner. Moreover, targeted Tir G-loop mutations (predicted to impair ATP binding) markedly reduced TNP-ATP binding affinity. To assess the Tir G-loop's relevance to EPEC virulence, we evaluated bacteria expressing Tir G-loop variants in an in vitro cell culture infection model. Notably, Tir G-loop mutations demonstrated to disrupt TNP-ATP binding resulted in a virulence defect, indicating that the Tir G-loop contributes to EPEC pathogenesis.

These data support a model in which a conserved G-loop in Tir functions as an ATP-binding motif and contributes to EPEC virulence. The findings reveal a previously unrecognized EPEC virulence mechanism with potential for therapeutic targeting through small-molecule ATP-binding site inhibition.

Peroxisome Lipid Metabolism Is a Central Regulator of TNF/IMD Signaling in Macrophages

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Introduction: Chronic inflammatory diseases affect millions of Canadians, with conditions like inflammatory bowel disease and arthritis causing significant health and socioeconomic burdens. Chronic inflammation is characterized by elevated cytokine levels, particularly tumor necrosis factor-alpha. While anti-TNF therapies can offer relief to some patients, their limited effectiveness and loss of response highlight the need for alternative treatment strategies.

Immune signaling pathways, including the TNF pathway, rely on the physical assembly of adaptor proteins into amyloid-like structures. In this pathway, the RIPK1 and RIPK3 form amyloid-like necrosomes that amplify inflammatory signaling. Similarly, the IMD pathway in *Drosophila melanogaster,* which is analogous to the mammalian TNF pathway, forms functional amyloids upon immune stimulation, thereby activating the signaling cascade and inducing the expression of distinct immune mediators. Our lab discovered that peroxisomes, organelles central to lipid metabolism, are vital for IMD activation. In this research, we focused on exploring a new regulatory mechanism that targets the assembly of immune signaling proteins during pathway activation.

Methodology: We employed *Drosophila* as a model system to investigate the molecular mechanisms underlying IMD pathway activation. Lipidomic analyses were conducted to assess changes in lipid composition in wild-type and peroxisome-deficient *Drosophila* macrophage-like cells, followed by targeted genetic manipulations to restore specific lipid species in peroxisome-deficient cells. Results were visualized with immunofluorescent microscopy, and pathway activation was confirmed by qPCR.

Results: Our findings reveal that peroxisome dysfunction disrupts IMD amyloid-like structures, thereby impairing immune activation. Lipidomic profiling indicated alterations in cellular lipid composition, particularly in glycerolipid intermediates. Remarkably, restoring diacylglycerol levels rescued IMD aggregation and immune mediator expression in peroxisome-deficient cells, demonstrating that specific lipids can directly modulate immune signaling by influencing protein assembly.

Conclusion: These results identify a previously unrecognized lipid-dependent regulatory mechanism controlling amyloid-like immune signaling complexes. This mechanism could open new avenues for developing innovative lipid-based strategies to manage chronic inflammatory diseases.

Funding: *This work was supported by the Molly Appeal Fund through the Dalhousie Faculty of Medicine 2025 Graduate Studentship program and CIHR project grant*.

Effects of Propofol in Addition to Isoflurane Anesthesia on the Immune Response within the Microcirculation: An Intravital Microscopy Study

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Background: Volatile as well as intravenous anesthetics have been reported to exert immunomodulatory effects that may influence inflammatory responses and microcirculatory function during and after surgery. Because inflammatory signaling and leukocyte–endothelial interactions play a key role in host defense and postoperative outcomes, understanding how anesthetic regimens affect immune responses is clinically relevant. However, the effects of combining inhalational and intravenous anesthetics on the inflammatory response remain insufficiently understood.

Methods: Twenty male C57BL/6J mice were randomly assigned to receive either isoflurane anesthesia alone or a combination of isoflurane and propofol. Under general anesthesia, animals were challenged with lipopolysaccharide (LPS) to induce an inflammatory response while control animals received saline injection. Intravital fluorescence microscopy of the intestinal submucosal microcirculation was used to quantify leukocyte rolling flux and leukocyte adhesion in collecting (V1) and post-capillary (V3) venules. In addition, functional capillary density (FCD) was measured in the intestinal mucosa and muscularis layers as an indicator of microvascular perfusion.

Results: Compared to isoflurane alone, propofol co-administration attenuated the inflammatory response to LPS by reducing leukocyte adhesion and partially preventing the decline in rolling in both V1 and V3. Intestinal FCD remained stable across both mucosal and muscular layers in both anesthetic regimens under baseline and inflammatory conditions.

Conclusions: Propofol appears to exert anti-inflammatory effects in the intestinal microcirculation during endotoxin-induced inflammation. The potential implications of these effects should be considered in situations involving pre-existing inflammation, where they may be protective, or during surgical trauma, where suppression of the physiological inflammatory response could be detrimental.

New Applications of Microcirculatory Methods

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Infrasound refers to sound below the human hearing range of 20 Hz and is emitted by many everyday structures. It is hypothesized that infrasound may activate PIEZO1 and PIEZO2 ion channels, which sense mechanical forces like pressure and vibrations, leading to various downstream effects such as Ca^{2+} and NO release. As a result, alterations in the microcirculation may occur. C57BL/6 mice (6-8 weeks old) were exposed to 100 dB/1 Hz infrasound for 4 hours. Baseline and post-exposure measurements of vasomotion and flow motion of the sublingual blood vessels were made using Sidestream Dark Field imaging (SDF) and Laser Doppler Flowmetry imaging (LDF), respectively. Results from both methods were then analyzed using Fast Fourier Transform (FFT) to be separated into three frequency bands: very low (0.005-0.15 Hz), low (0.15-2 Hz), and high (2-8 Hz), which correspond with endothelial/myogenic, respiratory, and cardiac activity, respectively. Significant increases in vasomotion were observed in the low and high frequency bands, while flow motion was significantly increased in the very low frequency band. Overall, an increasing trend in both vasomotion and flow motion was shown in all frequency bands. These results demonstrate that infrasound causes physiological changes in the microcirculation. Further research is needed to determine if these effects are pathological or reversible, and whether these effects of infrasound can be therapeutic in controlled settings.

Alternative quadruplex real-time PCR reactions for detection and discrimination of *Streptococcus pneumoniae* serotypes within serogroup 6

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Background. *Streptococcus pneumoniae* causes significant morbidity and mortality worldwide, and serotyping is important to assess the burden of disease that is vaccine preventable. For serotyping, the Centers for Disease Control and Prevention (CDC) use a series of 12 quadruplex real-time PCRs; however, reaction 5 (i.e., for detection/discrimination of serotypes 6A, 6B, 6C, and 6D) often failed. This study investigated the cause of the PCR failure and provided alternative PCRs to resolve this issue.

Methods. Quadruplex PCR target sequences were compared to *S. pneumoniae* reference genomes. The traditional PCR reaction 5 [6ABCD, 6AB, 6BD, and 6CD] and 11 [37, 10F, 11BC, and 18CFBA] were compared to alternative PCRs A1 [6ABCD, 10F, 11BC, and 18CFBA] and A2 [37, 6AB, 6BD, and 6CD]. All PCRs were tested using 10-fold serial dilutions of DNA from representative serotypes, and analytical specificity was assessed using DNA from other *S. pneumoniae* serotypes or various streptococci and Gram-positive cocci.

Results. Failure of the quadruplex PCR reaction 5 was associated with overlapping 6ABCD and 6BD targets. The separation of 6ABCD and 6BD targets in the alternative quadruplex PCRs A1 and A2 allowed sensitive and specific detection of serotypes 6A, 6B, 6C, and 6D, without impacting detection of serotypes 10F, 11BC, 18CFBA, and 37.

Conclusions. This study highlights the importance of rigorous author and peer-review to avoid manuscript errors and unintended consequences. By explaining what caused PCR failure, and proposing alternative quadruplex PCRs, this study demonstrates the value of scientific collaboration to ensure molecular assays best serve the scientific community.

Pseudomonas aeruginosa LasB activates autophagy and the ISR kinase GCN2

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Abstract:

Pseudomonas aeruginosa is a Gram-negative bacterium and opportunistic pathogen and the most common pathogen to cause chronic lung infection in CF patients. *P. aeruginosa* secretes an abundance of virulence factors including proteases and elastases that, in combination with exacerbated lung inflammation, cause significant damage to host lungs. Due to *P. aeruginosa*'s intrinsic and acquired antibiotic resistance, and lack of recent antibiotic development, alternative therapies to alleviate the consequences of *P. aeruginosa* infection are urgently needed. Our lab has found that inhibiting the integrated stress response (ISR) reduces the secretion of pro-inflammatory cytokines during *P. aeruginosa* infection. Therefore, the ISR is a promising therapeutic host target to alleviate some of the damaging inflammation during infection. The ISR is a highly conserved eukaryotic signalling pathway that responds to different types of cellular stress. Stress is sensed by four sensor kinases: heme regulated eIF2α kinase (HRI), RNA-dependent protein kinase (PKR), PKR like ER kinase (PERK), and general control non-derepressible (GCN2). Once activated, all kinases act to phosphorylate the eukaryotic translation initiation factor 2 alpha (eIF2α) which inhibits general protein synthesis but allows for the select translation of ISR effectors including activating transcription factor 4 (ATF4).

The *P. aeruginosa* secreted protease alkaline protease (AprA) was previously shown to activate the ISR. To follow up on this work, we treated the human cell lines A549, 16HBE, or THP-1 with purified secreted proteases and assessed the levels of ISR markers via western blotting. In this study, we confirmed previous AprA data and found that the following three secreted proteases also activate the ISR: elastase A (LasA), elastase B (LasB), and protease IV (PrpL). Additionally, by using cell lines which lack one of the ISR kinases, we determined that GCN2 was required for LasB to activate the ISR. Activation of the GCN2-ATF4 signalling axis has been linked to autophagy which led us to assess the accumulation of the classic autophagy marker LC3-II. Wildtype (WT) and GCN2$^{-/-}$ 16HBE cells were pre-treated with chloroquine (Cq), an inhibitor of autophagic flux, and LasB. Interestingly, autophagy induction was not dependent on GCN2. Additionally, we found that LasB was able to induce LC3-II accumulation in the macrophage cell line THP-1, indicating that this phenotype is not cell type specific. Finally, we have utilized an aqueous two-phase system (ATPS) to model *P. aeruginosa* infection with 16HBE cells for up to 16 hours. In this model, we have assessed the protein levels of p62, another autophagy marker, via western blotting. We have found that *P. aeruginosa* strains lacking LasB results in a delayed induction of autophagy in 16HBE cells compared to LasB expressing strains. These results suggest LasB has an important role in the timing of autophagy induction during *P. aeruginosa* infection.

NKR-P1B restrains glycolytic and inflammatory reprogramming of alveolar macrophages

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Alveolar macrophages (AMs) are the primary sentinel immune cells in the alveolar niche that protect against pathogens but are also uniquely adapted for debris clearance and surfactant metabolism to maintain lung homeostasis. We previously observed that the NK cell-associated receptor, NKR-P1B, is expressed by AMs and is critical for AM survival and metabolic reprogramming. To further elucidate the underlying mechanisms, we investigated the role of this receptor in AM metabolism and inflammation. Nkrp1b-/- mice display dramatically altered AM metabolism compared to wild-type (WT) mice. At steady state, while AMs from WT mice rely on mitochondrial oxidative phosphorylation, AMs from Nkrp1b-/- mice derive about 80% of their ATP through glycolysis. This metabolic shift is driven by the upregulation of the glucose transporter GLUT1 and hexokinase 1 (which is the key rate-limiting enzyme for glycolysis) in Nkrp1b-/- AMs. To characterize their phenotype further, we performed single-cell RNA sequencing of the AMs. Transcriptomic analysis revealed five major AM subpopulations in the lungs. The Ki67hi proliferating AM subpopulations are dramatically reduced in Nkrp1b-/- mice, explaining the decline of AM numbers. Another AM subset, which exhibits upregulated expression of genes related to hallmark inflammatory pathways and oxidative stress, is markedly enriched in the Nkrp1b-/- mice. We next validated the pro-inflammatory phenotype of these AMs through their phospho-kinome profiling, where we found that AMs from Nkrp1b-/- mice have several upregulated phosphorylated targets associated with inflammatory signalling. Together, our findings indicate that NKR-P1B restrains the glycolytic and inflammatory reprogramming of alveolar macrophages, thereby maintaining lung homeostasis.

Early Innate Immune Signatures Imprint Clinical Outcomes of *Bordetella pertussis* challenge in a Controlled Human Infection Model

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Background: Despite widespread vaccination, *Bordetella pertussis* continues re-emerging globally, highlighting gaps in understanding vaccine-induced protective immunity. Controlled human infection models (CHIMs) offer powerful platforms to interrogate host-pathogen interactions, define protection correlates, and inform next-generation vaccine design.

Methods: This open-label, phase 1, dose-escalation CHIM trial was conducted at the Canadian Center for Vaccinology. Healthy adults (18-40 years) were intranasally inoculated with *B. pertussis* isolate D420. Blood, serum, PBMCs, and nasal washes were collected at baseline and post-challenge. Innate immune responses were assessed using multicolor flow cytometry and Luminex assays, analyzed by clinical outcome, sex, and vaccination history.

Findings: Although infection followed dose-dependent patterns, 22% (11/50) of participants remained non-infected across all challenge doses, indicating intrinsic resistance to colonization of *B. pertussis*. Non-infected participants exhibited sustained expansion of circulating NK cells together with early mucosal production of granzyme A, granzyme B, IL-29 (type III interferon lambda 1), and MCP-2, reflecting rapid cytotoxic and antiviral-like effector programming associated with spontaneous clearance. In contrast, symptomatic participants displayed robust complement activation and mucosal production of eotaxin-2 and MIP-1δ, accompanied by depletion of circulating neutrophils and expansion of monocytes, eosinophils, and NK cells in peripheral blood. Asymptomatic individuals displayed a distinct intermediate phenotype**,** characterized by early I-TAC and TRAIL production with concurrent depletion of circulating neutrophils**.** *In vitro* assays further demonstrated that *B. pertussis* directly induced NK cell activation and degranulation, promoting production of granzymes, perforin, and IFN-γ together with CD16 upregulation. Importantly, NK responses induced by *in vitro* stimulation followed an intrinsic functional hierarchy aligned with clinical outcomes, being strongest in non-infected participants, intermediate in asymptomatic individuals, and weakest in symptomatic participants.

Interpretation: Distinct early innate immune programs are mechanistically linked to divergent clinical trajectories following *B. pertussis* challenge

Defining the contribution of microbiota-derived signaling to intestinal inflammation and neurodegenerative diseases

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Introduction: Neuroinflammation is an inflammatory response within the central nervous system (CNS) that arises in response to neuronal injury, infection, or stress. While inflammation has a protective role, inappropriate or prolonged inflammation in the brain can lead to neurodegenerative diseases such as Alzheimer and Parkinson. Peroxisomes are essential metabolic organelles that maintain cellular redox balance and regulate lipid metabolism, processes that are closely linked to immune cell function and inflammatory control. Consequently, peroxisomal dysfunction can disrupt immune regulation and promote neuroinflammation. Consistently, peroxisomal metabolic alterations have been observed in patients with neurodegenerative diseases. Preliminary research found that peroxisome alterations affect how the gut processes lipids and, consequently, alter the gut microbiota. Recent evidence further links changes in intestinal microbiota to neuroinflammation and neurodegeneration over aging. We hypothesize that impaired peroxisome function within intestinal cells alters the gut microbiome, creating an inflammatory environment that contributes to neurodegenerative diseases.

Methodology: *Drosophila melanogaster* was used as a model to study neurodegeneration and host-commensal interactions. To explore the differences in gut microbes, metatranscriptomics, and metabolomics analysis were performed in flies that have no functional peroxisomes only in the gut cells compared to wild-type. To validate these findings, microbe-specific primers were designed to target the most significantly abundant bacterial taxa, and behavioral assays were used to assess neurodegenerative phenotypes in response to changes in microbiota.

Results: metatranscriptomics results revealed substantial shifts in microbial composition in mutant flies. The most notable differences were observed in the *Acetobacter*, *Lactobacillus*, and *Pseudomonas* families. qPCR results confirmed that *Lactobacillus* and *Acetobacter* are the two major genera consistently altered. Additionally, climbing assay comparing mutant and wild-type flies demonstrated impaired locomotion in male mutants.

Conclusions: By identifying key bacterial metabolites contributing to neurodegeneration, this research could lead to new treatments targeting the gut microbiome, potentially slowing or preventing these diseases. Ultimately, the goal is to validate the finding in patients' fecal samples to link changes in the metabolism of selected microbes to the onset of neurodegeneration. This research aims to improve the quality of life for affected individuals and reduce the global healthcare burden.