New Frontiers in Infectious and Inflammatory Diseases

MCGILL UNIVERSITY RESEARCH CENTRE ON COMPLEX TRAITS (MRCCT) SYMPOSIUM

WEDNESDAY, DECEMBER 1, 2021

8:45 A.M. – 2:30 P.M.

New Frontiers in Infectious and Inflammatory Diseases

This symposium presents ongoing innovative research performed by new and senior MRCCT investigators, as well as by international speakers who are leaders in the study of inflammatory diseases and their development.

Organizing committee:

Martin Olivier (Chair),
Danielle Malo (Co-Chair),
Corinne Maurice and
Salman Qureshi

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Introductory remarks: Dr Martin Olivier & Dr Danielle Malo
Opening remarks: Dr Marie Hudson and Dr Silvia Vidal

SESSION 1 - Host Microbe Interaction in Health and Diseases
9:00am – 10:30am

 Chairs: *Angella Mingarelli & Dhanesh Patel*

9:00-9:30am: **Dr Gretchen Diehl** *(Sloan Kettering Institute, NY)*
             "*Thymic development of gut microbiota associated T cells"*
9:30-10:00am: **Dr Corinne Maurice** *(Dept. of Micro & Immuno, McGill University)*
             "Using bacteriophages to modulate the gut microbiome"
10:00-10:10am: **Questions for Speakers**

10:10-10:20am: **Students' presentation** (3 student talks/3 minutes)
             -Elizabeth Siciliani, Jessica Pei & Lindsay Burns
10:20-10:25am: **Questions for students**

10:30-10:45am: **BREAK** (15 min)

Chairs: *Amy Dagenais & Viktoria Plackoska*

10:45-11:15am: **Dr Judith Mandl** *(Dept. of Physiology, McGill University)*
          "Peering through a cell migration lens at type-2 helper responses"
11:15-11:45am: **Dr Ciriaco Piccirillo** *(Dept. of Medicine, McGill University)*
          "Functional adaptation of Foxp3+ regulatory T cells in health and disease"
11:45-11:55am: **Questions for Speakers**
11:55-12:05pm: **Students' presentation** (3 student talks/3 minutes)
          -Marine Rousseau, June Kim & Aanya Bhagrath
12:05-12:10pm: **Questions for students**

12:15-12:45pm: **BREAK** (30 min)

Dr Gretchen Diehl

Sloan Kettering Institute, NY

Research

The intestinal immune system faces a number of unique challenges due to continuous exposure to rapidly changing exogenous factors including diet and intestinal microbes. Proper calibration of responses is needed to clear invading pathogens as well as repair damage. Over enthusiastic responses within the intestine impair barrier repair, amplifying damage and potentially lead to systemic infection or chronic inflammatory disease including inflammatory bowel disease (IBD). We find that the intestinal microbiota and dietary factors can promote or inhibit proper immune regulation. As such, we seek to define molecular and cellular pathways regulated by the microbiota, dietary, and tissue factors that are required to maintain homeostasis within the intestine. In defining upstream signals, we are working to understand microbial pathways and how they modulate tissue immunity. In parallel, we seek to delineate how these networks are disrupted in inflammatory conditions.

Dr Corinne Maurice

Dept. of Micro & Immuno, McGill University

Dr Maurice is an Assistant Professor in the Department of Microbiology and Immunology at McGill University, a Tier 2 Canada Research Chair in gut microbial physiology, and an Azrieli Global Scholar. Her work aims to identify how to manipulate the human gut microbiome for health benefits, by characterizing the active bacterial subset of the human gut microbiome and determining how bacteriophages regulate it. Her expertise in single-cell tools and metagenomics have allowed her to pioneer the FACSeq method, whereby bacterial cells with distinct activity or damage can be sorted and sequenced to better characterize functional changes in this dynamic community. By applying microbial ecology concepts and tools to the study of bacteria and phage interactions, her group is currently exploring the role of bacteriophages in health, child stunting, and adult IBD

Dr Judith Mandl

Dept. of Physiology, McGill University

Dr Mandl is an Assistant Professor in the Department of Physiology, an associate member in the department of Microbiology and Immunology, and a member of MRCCT. She currently holds a Tier 2 Canada Research Chair in Immune Cell Dynamics and was recently awarded the New Investigator Award by the Canadian Society for Immunology. Since starting her lab at McGill in 2015, she has built on her expertise in cellular immunology, studying the complex migration choreography of immune cells that is critical to effective immune responses, with a particular focus on T cells. Her research focuses on the specific challenges T cells face as they move in tissues, to what extent nuclear deformability and cytoskeletal processes define how T cells make decisions as they navigate, the consequences of perturbing immune cell migration for T cell function and differentiation, and the specific interactions made by T cells during their migration which leads to heterogeneity in their behaviour. Her lab applies state-of-the-art microscopy and systems biology tools, using mouse models to link aspects of individual immune cell migratory behaviour to both within-cell cytoskeletal processes and whole organismal-level readouts such as cell differentiation, homeostasis and responses to infection.

Dr Ciriaco Piccirillo

Dept. of Medicine, MUHC

Dr. Piccirillo is a Professor in the Department of Microbiology and Immunology of McGill University and principal investigator of the MRCCT. He is the Director of the Centre of Excellence in Translational Immunology (CETI) at McGill and MUHC, and Senior Scientist in the Program in Infectious Diseases and Immunity in Global Health (IDIGH). Finally, he is the Director of the ImmunoPhenotyping Platform for the RI-MUHC. Dr. Piccirillo leads an internationally recognized research program which focuses on the regulation of T cell responses mediated by Foxp3+ regulatory T cells in autoimmune, infectious and inflammatory diseases. His research is responsible for many seminal and pioneering studies on the biology and function of Foxp3+ regulatory T cells in a variety of animal models, non-human primates, and humans. His current research program makes use of a variety of mouse models and in human subjects to monitor and characterize the development and functional dynamics of regulatory T cell function in lymphoid and non-lymphoid tissues in various inflammatory settings. His research program also focuses on the development of novel immunotherapeutic strategies to monitor and manipulate Foxp3+ regulatory T cells function and ultimately modulate immune responses in infectious, autoimmune, and inflammatory disorders, cancers or immunodeficiencies.

Dr David Langlais

Dept. of Human Genetics, McGill University

Dr Langlais is an Assistant Professor in the Department of Human Genetics at McGill University and Principal Investigator at the McGill Genome Centre. Dr Langlais completed his Ph.D. with honours in Molecular Biology under the supervision of Dr. Jacques Drouin at the Institut de recherches cliniques de Montréal. His work revealed the complex transcriptional regulation and tissue maintenance mechanisms at the immuno-neuroendocrine interface. Dr Langlais then pursued postdoctoral research in Dr Philippe Gros' laboratory at McGill University where he studied the role of critical innate immunity transcription factors and participated in the characterization of new genes involved in immune function and neuroinflammatory conditions. Dr Langlais has received multiple awards and fellowships, including the Milstein Young Investigator Award form the International Cytokine and Interferon Society. His current research is founded on functional genomics, bioinformatics, genome editing and molecular biology methods to explain the transcriptional mechanisms involved in normal and pathological inflammation, aiming to identify and validate novel therapeutic targets for inflammatory diseases.

Dr Jean-Laurent Casanova
Rockefeller University, NY

Research

Dr Casanova Lab studies how human genes determine the clinical manifestations and outcome of primary infections by viruses, bacteria, fungi, and parasites. He searches for single-gene mutations that selectively compromise the immunity of otherwise healthy children and adults who are exquisitely vulnerable to specific infectious diseases, including the novel coronavirus (SARS-CoV-2). He thus characterizes the molecular, cellular, and immunological mechanisms of life-threatening infectious diseases.

Students' presentation
Abstract
Session 1

Elizabeth Siciliani

ISOLATION OF NON-POLAR METABOLITES IN EXCRETORY/SECRETORY PRODUCTS FROM A PARASITIC WORM AND THEIR POTENTIAL AS IMMUNOTHERAPY IN INFLAMMATORY BOWEL DISEASE

Elizabeth Siciliani[1], Mifong Tam[2], Joseph F. Urban, Jr.[3], Richard J. Martin[4], Fernando Lopes[1], Timothy G. Geary[1], Armando Jardim[1], and Mary M. Stevenson[2]

[1]Institute of Parasitology, McGill University, [2]Department of Microbiology and Immunology, McGill University, [3]USDA, and [4]College of Veterinary Medicine, Iowa State University

Helminth therapy in patients with autoimmune diseases such as multiple sclerosis and autoinflammatory diseases such as inflammatory bowel disease (IBD) shows promise in clinical trials. Excretory/secretory products (ESP) released by gastrointestinal (GI) nematodes have potent immunomodulatory effects on immune cells. Rather than administering live parasites, a more rational approach is to identify immunomodulatory molecule(s) in ESP and develop these as immunotherapy. We observed ESP from the GI nematodes Ascaris suum and Heligmosomoides polygyrus bakeri suppress LPS-induced TNF-α secretion and induce IL-10 secretion by murine bone marrow-derived macrophages (BMDM). Proteins as well as metabolites in ESP from A. suum have similar effects on BMDM. To identify the metabolite(s) responsible, ESP was separated into polar and non-polar (NP) metabolites. NP metabolites found to modulate BMDM were further separated by column chromatography and the bioactivity of the fractions assessed on BMDM. Using this approach, a metabolite fraction isolated from both parasites (NP25), had TNF-α suppressing and IL-10 enhancing effects on LPS-stimulated BMDM. To further characterize NP25, we investigated the immunomodulatory effects on PBMC. NP25 suppressed monocyte secretion of TNF-α in response to LPS and induced IL-10 secretion. The therapeutic effects of A. suum NP25 were studied using DSS-colitis in C57BL/6 mice. Treatment with AsNP25 resulted in significantly longer colons, a lower histopathology score, and decreased TNFα mRNA expression in colon tissue compared to colitic mice. Together, these data indicate that NP metabolite(s) in ESP modulate pro- and anti-inflammatory cytokines in vitro and in vivo and ameliorate disease in DSS-induced colitis in mice.

Students' presentation
Abstract
Session 1

Jessica Pei
INVESTIGATING THE ROLE OF INTESTINAL EPITHELIAL CELLS IN PARKINSON'S DISEASE
Jessica Pei [1,2], Christina Gavino[2], Dr. Samantha Gruenheid[1,2]
McGill Department of Microbiology and Immunology[1], McGill University Research Centre on Complex Traits[2]

The maintenance of intestinal homeostasis is an intricately regulated system. It is driven by intestinal epithelial cells (IECs) which provide a physical barrier between luminal contents and host tissue. However, in digestive disorders, functional or morphological damage of the intestinal epithelial barrier impedes gut health and causes increased susceptibility to infections. Notably, intestinal regulation has become of interest to Parkinson's Disease (PD) research, a primarily neurodegenerative disease. There is increasing evidence that PD involves gastrointestinal dysfunction, whereby intestinal symptoms like nausea, vomiting, and constipation are observed years before the development of motor dysfunction. Additionally, patients with inflammatory bowel disease are more likely to develop PD, and there is a correlation between gastrointestinal infections and PD incidence. Previous work completed by our group and collaborators demonstrated that mice genetically susceptible to PD, via Pink1 KO, did not exhibit motor phenotypes until infected with a gram-negative bacterium. This data suggests a clear association between the regulation of intestinal health in PD development. However, the extent and mechanisms relating to IEC involvement in perpetuating PD remains unclear. We hypothesize that IECs play a role in the early pathophysiology of PD. Our aim is to culture intestinal colonoids to model how IECs from Pink1 KO mice respond to gram-negative pathogens and LPS stimulation compared to WT mice. In addition, we aim to develop co-culture models with epithelial monolayers and immune cells to help elucidate the mechanisms of their interaction in PD. By investigating the role of the gastrointestinal tract, these studies carry important implications for understanding the initiation and progression of PD.

Students' presentation
Abstract
Session 1

Lindsay Burns

THE BACTERIAL VIRULENCE FACTOR NLEA UNDERGOES HOST-MEDIATED O-LINKED GLYCOSYLATION

Lindsay Burns[1], Natalia Giannakopoulou[1], Lei Zhu[1], Rufaida Hassan Khan[2], Sadjia Bekal[2], T. Martin Schmeing[3] and Samantha Gruenheid[1]
Department of Microbiology and Immunology and McGill Research Centre on Complex Traits, McGill University[1], Laboratoire de santé publique du Québec, Institut national de santé publique du Québec, Sainte-Anne-de-Bellevue[2], Department of Biochemistry and Centre de Recherche en Biologie Structurale, McGill University[3]

Enterohemorrhagic and enteropathogenic Escherichia coli (EHEC and EPEC) are gastrointestinal pathogens responsible for severe diarrheal illness across the world, resulting in more than 500 million illnesses and nearly 200,000 deaths each year. EHEC and EPEC belong to a group of Gram negative bacteria characterized by their ability to form "attaching and effacing" lesions during colonization and, upon adherence, inject proteins directly into host intestinal cells via the type III secretion system (T3SS). Injected bacterial proteins have a variety of functions, but generally alter host cell biology to favour survival and/or replication of the pathogen. Non-LEE encoded effector A (NleA) is a T3SS-injected effector of EHEC, EPEC, and the related mouse pathogen Citrobacter rodentium. Studies in mouse models indicate that NleA has an important role in bacterial virulence. However, the mechanism by which NleA contributes to disease remains unknown. We have determined that following translocation into host cells, a serine and threonine rich region of NleA is modified by host-mediated mucin-type O-linked glycosylation. Surprisingly, this region was not present in several clinical EHEC isolates. This is the first example of a bacterial effector modified in this way inside host cells. Using comparative sequence analysis, we designed a non-modifiable variant of C. rodentium NleA. When expressed in C. rodentium, non-modifiable NleA was indistinguishable from wildtype NleA in an acute mortality model but conferred increased fitness over the course of infection in mixed infections in C57BL/6J mice. We hypothesize that EHEC and EPEC use NleA to exacerbate disease and that its host-mediated modification modulates pathogenicity.

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Students' presentation
Abstract
Session 2

Marine Rousseau

ACTIVITIES OF A NEWLY IDENTIFIED CYTOKINE COMPLEX FROM THE IL-6/IL-12 FAMILY

Marine Rousseau (1,2,3), Véronique Laplante(2,3), Ulysse Nadeau(2), Sarah Pasquin(3), Sylvie Lesage(1,3), Jean-François Gauchat(2)

(1) Département de microbiologie, infectiologie et immunologie, Université de Montréal, (2) Département de pharmacologie et physiologie, Université de Montréal, (3) Centre de recherche de l'Hôpital Maisonneuve-Rosemont, Montréal

Cardiotrophin-like cytokine factor 1 (CLCF1) is a neurotrophic factor initially identified as a lymphocyte B stimulating factor. Mutations in CLCF1 cause type 2 Cold-Induced Sweating Syndrome, a severe multisystem disorder coupled with recurrent childhood infections. The CLCF1- CRLF1 composite cytokine mediate its neurotrophic effects via the CNTF receptor (CNTFR). Although immune cells do not express CNTFR, immunological activities of CLCF1 have been described, suggesting the existence of an alternative receptor. Preliminary results suggest that CLCF1 can associate with the Epstein-Barr virus-induced gene 3 (EBI3). EBI3 is a subunit of the composite cytokines IL-27, IL-35 and IL-39, which exhibits immunoregulatory functions. Our hypothesis is that CLCF1 associates with EBI3 to activate an alternative receptor expressed by immune cells. The aim of the project is to identify the cells producing CLCF1/EBI3, to define its receptor and to characterize the influence of CLCF1/EBI3 on lymphocyte proliferation, differentiation and function. Our initial results show that EBI3 and CLCF1 can associate in the extracellular medium to form a complex. Moreover, we found that CLCF1/EBI3 can bind IL12Rß1, IL23R and CNTFRα receptor chains. Altogether, this data strongly suggests that the CLCF1/EBI3 complex is likely to assemble in vivo and act as a cytokine through known receptor chains. Overall, defining the cellular targets and biological activities of CLCF1/EBI3 will pave the way for the development of treatments in autoimmune diseases involving CLCF1 and EBI3, adding to the increasing number of biologic drugs targeting cytokines, their receptors, or signaling pathways that are used clinically to treat inflammatory diseases.

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Students' presentation
Abstract
Session 2

June Kim

MECHANISMS OF INTERSTITIAL LUNG DISEASE IN SYSTEMIC AUTOIMMUNE RHEUMATIC DISEASES

Jooeun (June) Kim[1,2], Lin Tze Tung[1,2], Mathieu Mancini[2,3], Mitra Yousefi[2,4], Inés Colmegna[5,6], Marie Hudson[5,7], Deborah Assayag[5,6], Danielle Malo[2,8], David Langlais[2,3,8], Silvia Vidal[2,8], Anastasia Nijnik[1,2]

Department of Physiology, McGill University[1], McGill University Research Centre on Complex Traits (MRCCT)[2], McGill Genome Centre[3], TCP Infection & Inflammation Core Facility, McGill University[4], Department of Medicine, McGill University[5], McGill University Health Centre (MUHC)[6], Lady Davis Institute for Medical Research, Jewish General Hospital[7], Department of Human Genetics, McGill University[8].

Systemic autoimmune rheumatic diseases (SARDs) involve immune dysregulation and a disruption to self-tolerance. Typical SARDs include rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), systemic sclerosis (SSc) and autoimmune myositis (AIM). Among the various organ systems that can be affected, the lungs are a common target of autoimmune-mediated injury within SARDs. Characterized by lung inflammation and fibrosis, interstitial lung disease (ILD) is a major cause of morbidity and premature mortality in SARDs patients. ILD among patients with SARDs varies widely in time course, morphological pattern, disease severity, as well as the specific immune components that mediate lung damage. It remains a major challenge to predict SARDs patients that will progress to develop ILD. In addition, the causes and mechanisms underlying SARDs-ILD remain largely unknown. To address this knowledge gap, we are performing broad immunophenotyping of immune cells on blood samples from SARDs patients with and without ILD, as well as age and sex-matched healthy controls. Similarly, detailed immunophenotyping will be performed on immune tissue, bone marrow, and lungs from different mouse models of SARDs, including the collagen-induced arthritis (CIA) model and the SKG-ILD model. By investigating immune cell numbers, activation, and polarization between different experimental groups in both patients and mouse models, we hope to better understand the immune mechanisms associated with the development of ILD in SARDs. These findings will have important implications for the prediction of disease onset and progression, and for the development of novel treatments for ILD in SARDs.

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Students' presentation
Abstract
Session 2

Aanya Bhagrath
AGE-RELATED CHANGES TO LYMPH NODE MICROARCHITECTURE AND IMPACTS ON T CELL RESPONSES

Aanya Bhagrath[1,2], Shabaz Sultan[3], Dr. Johannes Textor[3], Dr. Judith Mandl[1,2,4]

McGill Department of Physiology[1], McGill University Research Centre on Complex Traits[2], Radboud Institute for Molecular Life Sciences Department of Tumor Immunology[3], McGill Department of Microbiology & Immunology[4]

The COVID-19 pandemic has highlighted the tremendous role that age plays in disease outcome after infection. While weakened adaptive immunity in elderly people is partly attributed to the deterioration of the T cell response, known as immunosenescence, age-related changes in the lymphoid microenvironment in which T cells encounter antigen may also contribute to poor T cell responses. My research aims to better define age-related changes to lymph node (LN) microarchitecture and investigate how these lead to T cell immunosenescence. In the LN, T cells migrate along a stromal network composed of fibroblastic reticular cells (FRCs). Using custom-built machine learning algorithms, we have data suggesting that the ability of FRCs to stretch during an inflammatory response is impaired in aged mice, and so the LN cannot expand to the same capacity as in young mice. LNs of aged mice also show an accumulation of fibrotic extracellular matrix components through the FRC network, which may increase the mechanical stiffness of the LN. It is known that cells migrating through stiff environments accrue DNA damage, which is a hallmark of cellular senescence. Thus, I will measure LN tissue stiffness using a nanoindentor. I will then examine readouts of stiffness and DNA damage markers in T cells travelling through the lymphoid environments of both young and aged mice. Knowledge gained from my proposed research will improve our understanding of the underlying molecular mechanisms leading to T cell immunosenescence, which is crucial to developing more effective therapies for elderly individuals and helping to restore immunity.

Students' presentation
Abstract
Session 3

Dania Shaban

MYSM1 DEFICIENCY BONE MARROW FAILURE – INSIGHTS INTO DISEASE MECHANISMS FROM AN iPSCs MODEL

Dania Shaban[1,2], HanChen Wang [1,2], Yue Liang[1,2], Carol X.-Q. Chen[3], Philippe M. Campeau[4], Thomas Durcan[3], David Langlais[5], Anastasia Nijnik[1,2]
McGill University Research Centre on Complex Traits (MRCCT) [1]; Department of Physiology, McGill University[2]; Early Drug Discovery Unit, Montreal Neurological Institute, McGill University[3]; Centre Hospitalier Universitaire St. Justine Research Center, University of Montreal[4]; Department of Human Genetics and McGill Genome Centre, McGill University[5].

Hematopoiesis is the process that produces blood cells from bone marrow resident hematopoietic stem and progenitor cells (HSPCs). Careful regulation of this process is necessary for normal blood and immune system function, and many proteins and other factors are involved in maintaining this regulation. MYSM1 is a histone H2A K119-deubiquitinase that plays an important role in maintaining HSPCs and hematopoiesis in humans. Dysfunction of this gene leads to hematopoietic pathology and skeletal abnormalities, similar to ribosomopathy disorders like Diamond-Blackfan anemia and Shwachman-Diamond syndrome. Importantly, our team showed that in mouse HSPCs MYSM1 deficiency results in reduced expression of genes encoding ribosomal proteins, reduced protein synthesis, and induction of p53 dependent stress response. Based on these findings, we hypothesize that MYSM1 deficiency disorder in humans is a form ribosomopathy - a disease caused by dysfunctions in ribosome assembly and protein synthesis. However, to date, all work to explore this hypothesis has been based in mouse models and the mechanisms have yet to be validated in a human system. Here we established a human experimental system to study MYSM1 function, with isogenic iPSC lines: wild type, heterozygous, and homozygous for the MYSM1-p.S290* patient mutation, through CRISPR/Cas9 gene-editing. In my research project, the characterization of these iPSC models promises novel insight into the mechanisms of MYSM1 deficiency syndrome in human, which in the long term may facilitate the design of clinical therapies.

Students' presentation
Abstract
Session 3

Dakota Rogers

PRE-EXISTING CHROMATIN ACCESSIBILITY AND GENE EXPRESSION DIFFERENCES AMONG NAÏVE CD4^{+} T CELLS INFLUENCE EFFECTOR POTENTIAL

Dakota Rogers[1,2], Aditi Sood[3,4], HanChen Wang[1,2], Jasper J. P. van Beek[5], Caitlin Schneider[2,10], Connie Shen[2,10], Dylan Wong[2,10], Aanya Bhagrath[1,2], Andrew J. Martins[6], John S. Tsang[6], David Langlais[2,7,8], Heather J. Melichar[3,4], Johannes Textor[9], and Judith N. Mandl[1,2,10]

Department of Physiology, McGill University[1], McGill Research Centre for Complex Traits, McGill University[2], Immunology-Oncology Unit, Maisonneuve-Rosemont Hospital Research Center[3], Department of Medicine, Université de Montréal[4], Laboratory of Translational Immunology, Humanities Clinical and Research Center, Rozzano, Milan, Italy[5,] Systems Genomics and Bioinformatics Unit, Laboratory of Immune System Biology, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, USA[6], McGill University Genome Centre, Montreal[7], Department of Human Genetics, McGill University[8], Department of Tumor Immunology, Radboud Institute for Molecular Life Sciences, Nijmegen, The Netherlands[9] , Department of Microbiology and Immunology, McGill University[10].

CD4^{+} T cells have a remarkable potential to differentiate into diverse effector lineages following activation. We probed the heterogeneity present among naïve CD4^{+} T cells before encountering their cognate antigen to ask whether their effector potential is modulated by pre-existing transcriptional and epigenetic differences. Using single-cell RNA-seq, we showed that key drivers of variability were genes involved in T cell receptor (TCR) signaling and chromatin modification. Using CD5 expression as a read-out of the strength of tonic TCR interactions with self-peptide MHC, and sorting on the ends of this self-reactivity spectrum we performed bulk RNA- and ATAC-seq. There were 1006 differentially expressed genes between CD5^{lo} and CD5^{hi} cells, with ~2/3 upregulated in CD5^{hi} cells. Both RNA- and ATAC-seq datasets showed an enrichment of transcriptional regulators and chromatin modifiers in CD5^{hi} cells associated with follicular helper cell (T[FH]) responses. Moreover, CD5^{hi} cells were enriched for a T[FH] cell gene signature with increased gene expression of Bcl6, Cxcr5, Pdcd1, and decreased expression of Prdm1 that we showed impacted T[FH] versus non-T[FH] effector lineage choice upon infection in vivo. Interestingly, T cell deprivation of self-pMHC interactions identified transcriptional and chromatin differences between CD5^{lo} and CD5^{hi} cells that did not rely on continuous self-ligand interactions. Together, our data suggest that transcriptional and epigenetic differences in cell states among naïve CD4^{+} T cells impacts function upon activation. Ultimately, this may shed light on which pre-existing transcriptome-level differences are accessible to interventions targeting self-pMHC peripheral interactions, compared to others requiring modulation at the chromatin level.

Students' presentation
Abstract
Session 3

Monica Dallmann-Sauer

SINGLE-CELL PROFILING OF *MYCOBACTERIUM TUBERCULOSIS*-STIMULATED ALVEOLAR MACROPHAGES FROM PERSONS LIVING WITH HIV

Monica Dallmann-Sauer[1,2,3], Marianna Orlova[1,2], Pauline Cassart[1,2], Pauline Rivière[1], Ron Olivenstein[4], Josée Girouard[1,5], Jean-Pierre Routy[1,5], Wilian Correa-Macedo[1,2,6], Vinicius M. Fava[1,2], Erwin Schurr[1,2,3,6]

Program in Infectious Diseases and Immunity in Global Health, The Research Institute of the McGill University Health Centre[1]; McGill International TB Centre, McGill University[2]; Departments of Human Genetics and Medicine, Faculty of Medicine, McGill University[3]; Translational Research in Respiratory Diseases Program, The Research Institute of the McGill University Health Centre[4]; Chronic Viral Illnesses Service and Division of Hematology[5], McGill University Health Centre; Department of Biochemistry, Faculty of Medicine, McGill University[6].

Background: *Tuberculosis, caused mainly by Mycobacterium tuberculosis (Mtb), claims approximately 1.4 million lives every year, of which 15% are people living with HIV (PLWH). Alveolar macrophages (AMs) are the first immune cells to encounter Mtb upon inhalation of the bacilli. We previously showed that compared to healthy controls (HC) AMs from PLWH presented a weaker bulk transcriptome response to Mtb. In the present study, we aimed to track possible reasons for this weaker response on the single cell level.* ***Methodology:*** *As a pilot project, we obtained AMs by broncho-alveolar lavage from two HC and two PLWH study participants. Cells from each subject were kept uninfected or challenged with Mtb and incubated for 20h. To evaluate AM subpopulations, we employed single-cell RNA sequencing (scRNA-seq) using the 10X Chromium system. Seurat v3 and IKAP were used for data integration and unsupervised clustering, respectively. Differential expression analysis was done using the Wilcoxon test as implemented in Seurat.* ***Results:*** *We obtained 31.5k viable cells and identified three main subpopulations: One population of myeloid-derived macrophages and two populations of tissue-resident AMs (TR-AMs). Compared to HC, myeloid-derived cells and TR-AMs cluster 1 from PLWH showed weaker response to Mtb, while TR-AMs cluster 2 showed no response to the pathogen. The latter cluster was present at a higher proportion in PLWH subjects compared to HC. Our pilot scRNA-seq analysis suggested that not only PWLH displayed an overall reduced anti-mycobacterial response to Mtb, but also had a larger proportion of less responsive tissue resident AM.*