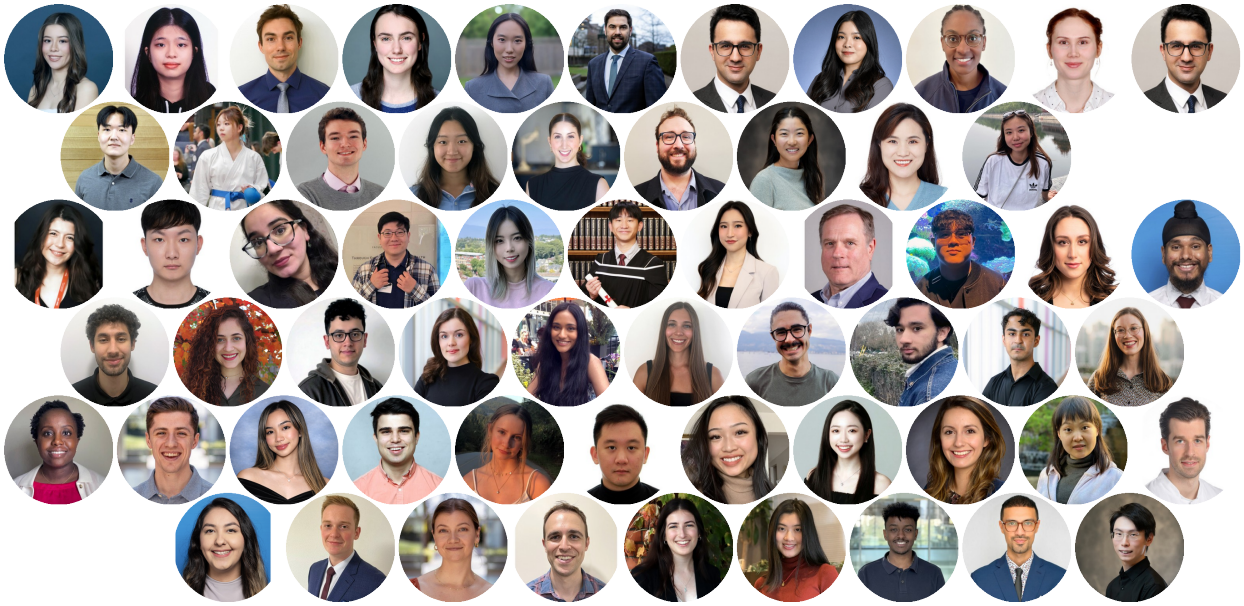
PATHDAY 2026

Research Highlights · Abstract Book

Department of Pathology and Laboratory Medicine · University of British Columbia



Thursday · June 4, 2026

BC Cancer Research Centre · MSAC
Vancouver, British Columbia

A day of presentations, posters,
and the people behind the science —
students, trainees, staff and faculty, together.

PATHDAY 2026

Acknowledgments

With gratitude to the committee, judges, and volunteers

Department of Pathology and Laboratory Medicine · University of British Columbia

PathDay 2026 is made possible by the dedication of our organizing committee, the generosity of our judges, and the hands-on work of our volunteers. Thank you all.

ORGANIZING COMMITTEE

Dr. Zu-hua Gao
Department Head

Dr. Inna Sekirov
Co-Chair

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Heather Cheadle

Sneha Dabgar

Dr. Shazia Masud

Guadalein Tanunliong

Kidus Achalu

Karina Martin

Dr. Cheryl Wellington

Karen Sherwood

Dr. Muhammad Morshed

Tetiana Povshedna

JUDGES

Oral Judges

8:10–9:00 am · Dr. Yemin Wang & Dr. Terry Jefferson
10:35–11:35 am · Dr. Diana Whellams & Dr. David Farnell
3:10–4:10 pm · Dr. Corrie Belanger & Dr. Steve E. Kalloger

Poster Judges (12:30–1:30 pm)

Undergrad · Dr. Shirsat & Dr. Masud (12:30–2:00)
Resident / PDF · Dr. Nouri & Dr. Yeung
PhD · Dr. Jassem & Dr. Mohamud
MSc · Dr. Tomalty & Dr. Uzozie

Noble Judges (1:30–2:30 pm)

BMLSc / Undergrad · Dr. Venturutti & Dr. Hutspardol
MSc · Dr. Velapatino & Dr. Yemin Wang
PhD · Dr. Ying Wang & Dr. Belanger
Residents / Med Students · Dr. Broderick & Dr. Whellams

VOLUNTEERS

Staff Volunteers

Jennifer Xenakis	· Noble Judges Organizer
Hannah Sauve	· Oral Judges Coordinator
Susanna O'Neil	· Breakfast Set-up & Morning Registration
Juliana Li	· Lunch Registration
Genevieve MacMillan	· Morning Registration
Lisa Robichaud	· Morning Registration
Annie Lin	· Poster Judge Coordinator & Certificates

Student Volunteers

John Perrier	· PhD
Wyatt Anderson	· PhD
Fatima Yaseen	· MSc
Maria Elishaev	· PhD
Cecilia Lee	· MSc
Rachel Pan	· BMLSc
Kidus Achalu	· PhD
Johnson Zhong	· BMLSc
Abbey Sugars-Keen	· MSc

PATHDAY 2026

Invited Speakers

Featuring three distinguished researchers in molecular pathology and genomics

Department of Pathology and Laboratory Medicine · University of British Columbia

PathDay 2026 is honoured to welcome three distinguished researchers whose work spans whole-genome oncology, pathogen genomics in public health, and emerging genomic diagnostics in hematopathology.

9:40 – 10:35 AM

Dr. Marcin Imieliński

Associate Professor, NYU · Director, Cancer Genetics & Genomics, Perlmutter Cancer Center

"A whole genome vision for molecular oncology"

Dr. Imieliński is a physician-scientist whose research focuses on patterns of complex, noncoding, and structural genomic variation in human cancer. He earned his MD and PhD at the University of Pennsylvania and completed residency and fellowship training in molecular genetic pathology at Massachusetts General Hospital and Harvard Medical School, followed by postdoctoral work at the Broad Institute and Dana-Farber Cancer Institute. His laboratory has pioneered novel "genome graph" methods (JaBBA, gGnome) and long-read assays (Pore-C) to study complex genomic rearrangements, and has identified noncoding mutational patterns linking cancers to their cells of origin. His current work expands the clinical utility of whole-genome sequencing in oncology.

2:40 – 3:10 PM

Dr. Natalie Prystajecky

Clinical Associate Professor, UBC · Program Head, BCCDC Public Health Laboratory

"From Sequence to Surveillance: The Coming of Age of Pathogen Genomics in Public Health"

Dr. Prystajecky leads the Environmental Microbiology and Molecular and Microbial Genomics laboratories at the BCCDC Public Health Laboratory and is a Clinical Associate Professor in Pathology and Laboratory Medicine at UBC. She uses pathogen genomics and other emerging technologies to strengthen public health surveillance, outbreak investigation, and laboratory response across a wide range of infectious diseases. Recent contributions include expanding sequencing capacity at the BCCDC, launching BC's wastewater surveillance program, and supporting genomic research on emerging pathogens such as H5N1. She is co-leading the development of a genomics core to expand access to sequencing technologies and applied genomics expertise.

4:10 – 4:40 PM

Dr. Eric McGinnis

Clinical Assistant Professor, UBC · Hematopathologist, Vancouver General Hospital

"Reading between the cells: Exploring genomic diagnostics in hematopathology"

Dr. McGinnis is a hematopathologist at Vancouver General Hospital and a Clinical Assistant Professor at UBC. He completed training in hematological pathology at UBC, followed by fellowship training in cancer cytogenomics and molecular pathology at VGH and BC Cancer. His work focuses on bringing genomic technologies — including next-generation sequencing and optical genome mapping — into everyday hematopathology practice, and on the potential of emerging genomic technologies to improve laboratory hematology. He is actively involved in teaching and clinical assay development in laboratory cancer genetics and is an advocate for enhancing trainee education in molecular diagnostics.

PATHDAY 2026

Event Schedule · Pacific Time | BC Cancer Research Centre & MSAC

BC Cancer Research Centre · Lunch Room

7:30 – 8:00 am Light Breakfast

BC Cancer Research Centre · Diamond Theatre

8:00 – 8:10 am

Welcome to PathDay 2026 & Land Acknowledgement

Dr. Gao
Opening Remarks — Frederica Di Palma

8:10 – 9:00 am

Trainee Presentations — Session I

Moderated by: Conor Broderick

8:10 – 8:20 am Kristen Danielle Go *(MSc student)*
8:20 – 8:30 am Kidus Achalu *(PhD student)*
8:30 – 8:40 am Sina Azad *(Resident)*
8:40 – 8:50 am Wyatt Anderson *(PhD student)*
8:50 – 9:00 am Zhihan Wang *(PhD student)*

9:00 – 9:25 am

PowerPitch Talks

Moderated by: Jared Taylor

BC Cancer Research Centre · Lunch Room

9:25 – 9:40 am **BREAK**

BC Cancer Research Centre · Diamond Theatre

9:40 – 10:35 am

Keynote Speaker

Marcin Imieliński

"A whole genome vision for molecular oncology"

10:35 – 11:35 am

Trainee Presentations — Session II

Moderated by: Jonathan Bush

10:35 – 10:45 am Cecilia Lee *(MSc student)*
10:45 – 10:55 am Fabian Frontzek *(PhD student)*
10:55 – 11:05 am Hasan Hamze *(Resident)*
11:05 – 11:15 am Cyril Helbling *(PhD student)*
11:15 – 11:25 am Khashayar Hanjani *(Resident)*
11:25 – 11:35 am Zeshuo Li *(PhD student)*

MSAC

11:45 am – 12:30 pm — **Networking for Trainees**
Pre-registered trainees only
Moderated by: Jared Taylor

12:00 – 2:30 pm — **Lunch & Poster Presentations**
Posters: 12:30 – 2:30 pm

BC Cancer Research Centre · Diamond Theatre

2:40 – 3:10 pm — **Keynote Speaker**
Natalie Prystajecky
"From Sequence to Surveillance: The Coming of Age of Pathogen Genomics in Public Health"

3:10 – 4:10 pm — **Trainee Presentations — Session III**
Moderated by: Ying Wang

3:10 – 3:20 pm Abbey Sugars-Keen *(MSc student)*
3:20 – 3:30 pm Jhunam Sidhu *(PhD student)*
3:30 – 3:40 pm Opeyemi Peluola *(Resident)*
3:40 – 3:50 pm Alexandra Witt *(PhD student)*
3:50 – 4:00 pm Mark Trinder *(Resident)*
4:00 – 4:10 pm Jenny Zhao *(PhD student)*

4:10 – 4:40 pm — **Keynote Speaker**
Eric McGinnis
"Reading between the cells: Exploring genomic diagnostics in hematopathology"

4:40 – 4:50 pm — Closing Remarks — Co-Chairs

MSAC

5:00 – 8:30 pm — **Awards Ceremony & Reception**

- BMLSc Awards
- Noble Awards
- Grad Program Awards
- PathDay Trainee Awards

Opportunity to Connect

How to use this book

Abstracts are listed in two sections — Oral Presentations followed by Poster Presentations — and numbered sequentially. Each entry includes the presenter's name, role, abstract title, and full author list. Affiliations for all authors are recorded in the master abstract file.

NOBLE 00 Indicates a Noble Award entry, with its assigned Noble abstract number

ORAL PRESENTATIONS

#	NAME	ABSTRACT
1	**KRISTEN DANIELLE GO** *MSc student*	**PROTEOMIC ANALYSIS OF BLOOD-BASED NEUROLOGICAL AND INFLAMMATORY BIOMARKERS IN CHRONIC COVID-19** K. Danielle Go[1,2], Jennifer G. Cooper[1,2], Sophie Stukas[1,2], Ryan L. Hoiland[2], William J, Panenka[2], Mypinder S. Sekhon[2], Nicholas A. Fergusson[3], Noah Silverberg[2], Edward M. Conway[1,4], Thalia S. Field[2,5], William Honer[6,7], A. Jon Stoessl[2], Donna J. Lang[2,6,7], Vesna Sossi[2,6], Cheryl L. Wellington[1,2,8,9]
2	**KIDUS ACHALU** *PhD student*	**IDENTIFYING BLOOD-BASED BIOMARKERS OF YOUTH SPORTS-RELATED CONCUSSION** Kidus Achalu BSc[1,2], Jennifer G. Cooper BMLSc[1,2], Jason B. Tabor, PhD[3,4,5], Mohammad Ghodsi BSc[1,2], Tessa Morelli[1,2], Johnny Huang BSc[1,2], Nik Josafatow-García MSc[3,4,5], Linden C. Penner MSc[3,4,5], Sophie, Stukas, PhD[1,2], Jean-Michel Galarneau PhD[3], Douglas D. Fraser MD PhD[6], Jonathan Smirl PhD[3,4,5], Keith Owen Yeates, PhD[4,5,7], Chantel T. Debert MD MSc[3,4,5,8], #Carolyn A. Emery PhD[3,4,5,9] and #Cheryl L. Wellington PhD[1,2,10]
3	**SINA AZAD** *Resident* **NOBLE 88**	**IDENTIFYING SOURCES OF FRICTION IN MASSIVE HEMORRHAGE PROTOCOL MANAGEMENT AT VANCOUVER COASTAL HEALTH: A RETROSPECTIVE MULTICENTRE ANALYSIS OF SAFETY EVENTS AND INCIDENT REPORTING** Sina Azad[1], Danielle Truong[2], Tara Winckler[2], Caroline Watt[2], Gaby Chan[2], Margaret Roche[2], Lawrence Sham[2], Tyler Smith[1,2], Jacqueline Trudeau[3], Alex Dotto[2,3], Sakara Hutspardol[1,2]
4	**WYATT ANDERSON** *PhD student* **NOBLE 73**	**KRAS AND STK11 MUTATIONS SHAPE IMMUNE INFILTRATION AND RESPONSE TO IMMUNOTHERAPY IN NON-SMALL CELL LUNG CANCER** Anderson, Wyatt[1,2,3]. Liao, Daniella[2,3] . Fong, Arwen[3]. Xiong, Will[1,3]. Fitzsimons, Evelyn[3]. De Souza, Vanessa[1,2,3]. Wu, Willie[2,3]. Enfield, Katey[1,2,3]
5	**ZHIHAN WANG** *PhD student* **NOBLE 74**	**UNRAVELING THE GENETIC FACTORS INFLUENCING SUSCEPTIBILITY AND RESISTANCE TO VIRAL MYOCARDITIS** Wang, Zhihan[1,2]; Yasir Mohamud[1,2]; Amrit Singh[1,3]; Tao Sun[1]; Honglin Luo[1,2]
6	**CECILIA LEE** *MSc student* **NOBLE 66**	**MODELING AND CHARACTERIZATION OF CYTOKINE RECEPTOR COMMON B CHAIN MUTATIONS IN MEDIASTINAL LYMPHOMAS** Cecilia Lee[1,2], Shinya Rai[3], Gerben Duns[2], Yifan Yin[2], Tomohiro Aoki[4], Grace Cheng[5], Sandra Spencer Miko[5], Gregg Morin[5], David Scott[2], Christian Steidl[2]
7	**FABIAN FRONTZEK** *PhD student*	**SOMATIC IRF4 MUTATIONS ENHANCE IL10-JAK-STAT3 SIGNALING IN**

		DIFFUSE LARGE B-CELL LYMPHOMA OF THE ABC SUBTYPE Fabian Frontzek[1,2], Gerben Duns[1], Michael Li[1], Shinya Rai[1], Rosalie Zhou[2], Jeffrey Niu[1], Jasper Wong[1], Amos Fong[1], Adèle Telenius[1], Claudia Cassidy[1], Laura Hilton[1], David W. Scott[1,2], Christian Steidl[1,2]
8	**HASAN HAMZE** *Resident* NOBLE 89	**REDUCING CARBAPENEM USE FOR LOW-RISK AMPC-PRODUCING ENTEROBACTERALES: IMPACT OF A MICROBIOLOGY COMMENT-BASED QUALITY INITIATIVE.** Hamze, Hasan[1], Amaral, Genevieve[1], Aloufi, Ahmad[2], Lo, Calvin[1], May, Stephanie[3], Grant, Jennifer[4,5], Yuen, Victor[1,3].
9	**CYRIL HELBLING** *PhD student*	**A DIGITAL ALPHA-SYNUCLEIN SEED AMPLIFICATION ASSAY** Cyril Helbling[1], Mari L. DeMarco[1,2]
10	**KHASHAYAR HANJANI** *Resident*	**SIMULATING SIGNIFICANCE: COMBINING BIOCHEMICAL TESTING WITH MOLECULAR DYNAMICS SIMULATIONS TO CHARACTERIZE VARIANTS OF UNKNOWN SIGNIFICANCE IN AN UNUSUAL CASE OF DOLICHOL KINASE DEFICIENCY** Théberge, Emilie[1] Hanjani, Khashayar[2] Monaghan, Jennifer[3] Rakic, Bojana[2] Sinclair, Graham[2] He, Miao[4] Roston, Thomas[5] Hawkins, Nathaniel[5] Lehman, Anna[1]
11	**ZESHUO LI** *PhD student* NOBLE 75	**INFLUENCE OF DNA EXTRACTION METHODS ON THE PREVALENCE OF LOW-FREQUENCY G>A MUTATIONS IN MITOCHONDRIAL DNA** Authors: Zeshuo E.S. Li[1,2], Hailey Chapman[1], Rachel Dunn[1], Loïc C. Caloren[1], Izabelle Gadawska[1], Maria S. Peñaherrera[3,4], Chelsea Elwood[5], Deborah M. Mone[5,6], Wendy P. Robinson[3,4], Hélène C.F. Côté[1,2,6,7]
12	**ABBEY SUGARS-KEEN** *MSc student*	**NEW INSIGHTS INTO THE THROMBOTIC COMPLICATIONS OF TYPE 2 DIABETES** Abbey Sugars-Keen[1], Paniz Ghavimi[1], Nooshin Safikhan[1], Kevin Gonzalez[1], Nathanael Caveney[2], Edward Conway[1]
13	**JHUNAM SIDHU** *PhD student*	**DEGRADOMIC ANALYSIS REVEALS NOVEL ROLE FOR GRANZYME K IN INFLAMMATION AND PSORIASIS** Jhunam Sidhu[1,2,3], Katlyn L. Richardson[1,2,3], Anna Prudova[1,2,3], Alexandre Aubert[1,2,3], David J. Granville[1,2,3]
14	**OPEYEMI PELUOLA** *Resident*	**MOLECULAR FEATURES ASSOCIATED WITH TUMOR BUDDING AND RECURRENCE IN LUNG SQUAMOUS CELL CARCINOMA** Opeyemi Peluola,[1] Cathy Yan,[2] Richard Corbett[2], Melanie Bailey[2], Zhou Fang,[3] Drew Smith,[1] Jennifer Ji,[1] Marco Marra[4,5], Julia Naso[1,6]
15	**ALEXANDRA WITT** *PhD student*	**IT TAKES TWO: ADJUNCT FACTOR X FOR SAFER CLOT LYSIS** Witt, Alexandra[1,2,3] Hao, Lihua[2,3] Pryzdial, Ed[1,2,3]
16	**MARK TRINDER** *Resident*	**IMMUNE REGULATORY GENE EXPRESSION PROFILING OF BRONCHOALVEOLAR LAVAGE SPECIMENS FOR DISTINCTION OF LUNG ADENOCARCINOMA FROM BENIGN LESIONS** Trinder, Mark[1], Wang, Peiyao[2], Lim, Emilia[3], Lockwood, Will[1,2], Naso, Julia R.[1,4]
17	**JENNY ZHAO**	**TMEM30A LOSS OF FUNCTION MUTATIONS IN B-CELL LYMPHOMA**

	PhD student NOBLE 76	**DIFFERENTIALLY IMPACT B CELL SUBSETS AND THEIR FUNCTIONALITIES** Zhao, Jenny[1,2,3], Cardoso, Miguel[1,3], Pijpers, Lizzy[1,3], Tang, Jing[1,3,4], Nawaz, Waqas[1,3], Venturutti, Leandro[1,2,3]

POSTER PRESENTATIONS

#	NAME	ABSTRACT
18	**LYNNE ALTOW** *Medical Student* NOBLE 79	**UNDER THE MICROSCOPE: STUDENT PERCEPTIONS OF PATHOLOGY PRACTICE, CAREER, AND CURRICULUM** Altow, Lynne[1] Povshedna, Tetiana[2] Zhao, Michael[1] Hopkins, Jade[1] Ionescu, Diana N.[2,3]
19	**TEJVEER ATWAL** *Medical Student*	**GENOME AND TRANSCRIPTOME SEQUENCING IN NON-SMALL CELL LUNG CANCER IDENTIFIES THERAPEUTIC OPTIONS BEYOND STANDARD OF CARE** Atwal, Tejveer[1], McConechy, Melissa[2], Csizmok, Veronika[2], Corbett, Richard[3], Chand, Damini[2], Nelson, Jessica[2], Laskin, Janessa[4], Marra, Marco[5,6], Naso, Julia[7,8]
20	**POLINA NOVOSELTSEVA** *Medical Student* NOBLE 80	**DRUGS VERSUS BUGS: CUMULATIVE ANTIMICROBIAL SUSCEPTIBILITY TESTING OF COMMUNITY-ACQUIRED BLOODSTREAM INFECTIONS IN BRITISH COLUMBIA** Polina Novoseltseva,[1] Romina Reyes,[1,2] and Dr. Eugene Y. H. Yeung[1,2,3,4]
21	**NIKI SADAT AFJEH** *Medical Student* NOBLE 81	**THE VANCOUVER GENERAL HOSPITAL GASTROINTESTINAL BIOBANK: SUPPORTING PANCREATIC CANCER RESEARCH** Niki Sadat Afjeh[1], Maya Kevorkova[2], Shanzhao Wang[2], Martin Avancena[2], Rachel Windardi[2], Bruno Larcoa[2], Steve Kalloger[2], David F. Schaeffer[2]
22	**JOSEPH SILBURT** *Medical Student* NOBLE 82	**DOES TUMOR ARCHITECTURE PREDICT MOLECULAR STATUS? EXPLORING THE APPLICATION OF NEURAL NETWORKS FOR HISTOLOGICAL FEATURE GENERATION** Silburt, Joseph[1], Rasmussen, Sean[2]
23	**PEIYAO WANG** *Medical Student*	**HIGHLY PM2.5 EXPOSED PATIENTS WITH LUNG ADENOCARCINOMA HARBOUR A DISTINCT MUTATIONAL SIGNATURE DERIVED FROM PM2.5 EXPOSURE IN LUNG EPITHELIAL CELLS** Wang, Peiyao[1] , Julia, Naso[2] , Myers, Renelle[2] , Durney, Clinton[2] , Granville, Joshua[1] , Chuang, Yu-Chi[1] , White, Justin[1] , Bartolomeu, Crista[1] , McGuire, Anna[2] , MacAulay, Calum[1] , Lam, Stephen[1] , Lam, Wan[1] , Lockwood, William[1]
24	**MICHAEL ZHAO** *Medical Student* NOBLE 83	**BRIDGING THE DIFFERENCE: MEDICAL STUDENT EXPERIENCES WITH HISTOPATHOLOGY IN AN INTEGRATED CURRICULUM** Zhao, Michael[1] Povshedna, Tetiana[2] Altow, Lynne[1] Hopkins, Jade[1] Ionescu, Diana N.[2,3]
25	**MEHAK JUDGE** *Undergrad*	**CHOLESTERYL ESTER TRANSFER PROTEIN (CETP) EXPRESSION IN 5XFAD MICE: MINIMAL EFFECTS ON PERIPHERAL LIPIDS AND AMYLOID-BETA PATHOLOGY** Mehak Judge[1,2], Tetiana Poliakova[1,2], Mehwish Anwer[1,2], Carlos Barron[1,2], Tom Cheng[1,2], Jianjia Fan[1,2], Anna Wilkinson[1,2], Cheryl Wellington[1,2,3,4]

26 **JIHYUN LEE**
BMLSc
NOBLE 61

RETROSPECTIVE STUDY OF HISTOPATHOLOGIC AND MOLECULAR RISK FACTORS FOR BRITISH COLUMBIA POPULATION COHORT OF ORAL DYSPLASIA

Lee, Jihyun[1] Liu, Kelly Y.P.[1,2] Saleh, Daniyah[3] Poh, Catherine F.[1,2,3] Ko, Yen Chen Kevin[1,2,3] Ng, Tony L.[1,3]

27 **JUSTIN WONG**
BMLSc
NOBLE 62

PROGNOSTIC MODELLING AND SPATIAL TRANSCRIPTOMIC ANALYSIS OF A 79-GENE IMMUNE PANEL IN GLIOBLASTOMA REVEALS C-TYPE LECTIN DOMAIN FAMILY 10 MEMBER A SPATIAL PATTERNS

Wong, Justin Amen[1] Ali Bashashati[1,2] Katherine Rich[3]

28 **MATTHEW YAP**
BMLSc
NOBLE 63

MARKER-SPECIFIC VALIDATION OF AN AUTOMATED IMMUNOHISTOCHEMISTRY H-SCORE QUANTIFICATION PIPELINE IN MUSCLE-INVASIVE BLADDER CANCER

Matthew Yap[1], Ioana-Maria Mihai[1,2], Maram Alanazi[2], Gheorghe-Emilian Olteanu[3], Alberto Contreras-Sanz[4], Peter Black[4], Gang Wang[1,2*]

29 **ABTEEN ARAB**
Undergrad

WHEN DO GLOMERULAR SEGMENTATION MODELS FAIL? A BENCHMARK OF GLOMERULAR SEGMENTATION IN PEDIATRIC, DISEASED, AND VARIABLY STAINED KIDNEY TISSUE

Arab, Abteen[1], Brown, Kelly[2,3], Morishita, Kimberly[2,3], Bashashati, Ali[1,4], Riazy, Maziar[4,5]

30 **DANIELLE KEITH**
Undergrad

EPSTEIN-BARR VIRUS DRIVES A TH1 PHENOTYPE IN A MOUSE MODEL OF PSORIATIC ARTHRITIS

Keith, Danielle[1] , Allanach, Jess[1,2], Horwitz, Marc[1,2]

31 **AHMED MAKHLOUF**
Undergrad
NOBLE 64

APPLICATION OF CUMULATIVE ANTIMICROBIAL SUSCEPTIBILITY DATA TO INFORM ORAL THERAPY IN JOINT INFECTIONS

Makhlouf, Ahmed[1]; Yeung, Eugene[1,2,3]

32 **DILNAR MAMATYUSUF**
Undergrad

ENHANCED ANTIBIOGRAM OF CARBAPENEM-RESISTANT UROPATHOGENS IN BRITISH COLUMBIA: A RETROSPECTIVE ANALYSIS

Dilnar Mamatyusuf[1], Eugene Y. H. Yeung[1,2,3]

33 **ALINA YU**
Undergrad
NOBLE 65

HOW DIET INFLUENCES ALZHEIMER'S DISEASE PATHOLOGY: AMYLOID-BETA PLAQUE QUANTIFICATION IN TRANSGENIC MICE MODELS

Alina Yu[1,2], Tetiana Poliakova[1,2], Anna Wilkonson[1,2], Mehwish Anwer[1,2], Carlos Barron[1,2], Tom Cheng[1,2], Jianjia Fan[1,2], Cheryl Wellington[1,2]

34 **GAEA LOUISE BUENAVENTURA**
MSc student

DEVELOPING A 3D CO-CULTURE MODEL TO STUDY CELLULAR RESPONSES FOLLOWING PERCUTANEOUS CORONARY INTERVENTION

Buenaventura, Gaea[1,2], Chatha, Aakar[1,2], Sun, Tao[2], Kong, Hyejin Julia[2], Elishaev, Maria[1,2], Samra, Amrit[2], Sahin, Basak[2], Walley, Keith[2,4], Lai, Chi[3], Yao, Yuan[2,5,6], and Wang, Ying[1,2]

35 **TIFFANY CHEN**
MSc student
NOBLE 67

UNDERSTANDING THE EFFECT OF FOLIC ACID ON BETA-CELL FUNCTION

Tiffany Chen[1], Zoe Lofft[1], Francis Lynn[2], Angela M Devlin[3]

36 **GAHAN DIWAN**
MSc student

GRANZYME B AS A DRIVER OF IMMUNOMODULATION AND ATROPHIC SCARRING IN DISCOID LUPUS ERYTHEMATOSUS

NOBLE 68

Diwan, Gahan[1,3,4], Crawford, Richard[1,2], Granville, David[1,3,4]

37 **TISHA HAUKONGO**
MSc student

INVESTIGATING LINE-1 EXPRESSION IN WOMEN LIVING WITH AND WITHOUT HIV

Haukongo, Tisha[1] Afe, Michael[1] Cai, Loulou[1] Gadawska,Izabelle[1] Kaida, Angela[2,3,5] King, Elizabeth M[2,3,4,5,8] Murray, Melanie CM[2,3,4,7,8] Cote, Helene CF[1,2,3,6,7] on behalf of the British Columbia CARMA-CHIWOS Collaboration (BCC[3]; CIHR CTN+[3,3,5])

38 **VIVIAN HO**
MSc student

PREDICTING THE CARDIOVASCULAR OUTCOMES OF ANTI-CANCER AXL INHIBITORS

Ho, Hsing-Wei[1,2], Elishaev, Maria[1,2], Buenaventura, Gaea L.[1,2], Mao, Yuancheng[1,2], Reece, Nina[1,2], Chatha, Aakar[1,2], Leung, Samuel[1,2], Sun, Tao[1,2], Kong, Hyejin Julia[1,2], Lai, Chi[1,2,3], and Wang, Ying[1,2].

39 **ZOE HORLICK**
MSc student

VALIDATION OF SERUM GLIAL FIBRILLARY ACIDIC PROTEIN AND NEUROFILAMENT LIGHT AS BIOMARKERS OF ACUTE SPINAL CORD INJURY

Horlick, Zoe L.[1], Morelli, Tessa[2], Stukas, Sophie[2], Gee, Cameron M.[1,3], Tsang, Angela[4], McKenzie, Miko[4], Belanger, Lise[4], Ritchie, Leanna[4], Ailon, Tamir[5], Dandurand, Charlotte[5], Paquette, Scott[5], Charest-Morin, Raphaële[3], Dea, Nicolas[5], Street, John[3], Fisher, Charles G.[3], Wilson, Jefferson[6], DiGiorgio, Anthony[7], Mac-Thiong, Jean-Marc[8], Christie, Sean[9], Wilson, Jamie[10,11], Ricks, Christian[1,2], Okonkwo, David[1,3], Kwon, Brian K.[1,3]

40 **CHRISTOPHER KIM**
MSc student
NOBLE 69

ADVANCING THE DIAGNOSIS OF MICROVASCULAR INFLAMMATION IN KIDNEY TRANSPLANTATION

Kim, Christopher[1,2], Bissonnette, Mei Lin[1,3], Martin, Spencer[4], Cheung, Honor[4], Sherwood, Karen[1,2], Keown, Paul[1,2,3], Huntsman, David[1,4], Lan, James[1,2,3]

41 **BOB LIN**
MSc student
NOBLE 70

UNDERSTANDING THE MECHANISM BEHIND COXSACKIEVIRUS-INDUCED NON-CANONICAL AUTOPHAGY: IMPLICATIONS FOR AMYOTROPHIC LATERAL SCLEROSIS PATHOLOGY

Lin, Bob[1,2] Luo, Honglin[1,2]

42 **ADAM MCGIVERN**
MSc student
NOBLE 71

IMPLEMENTATION AND ASSESSMENT OF DECENTRALIZED DONOR-DERIVED CELL-FREE DNA TESTING FOR KIDNEY TRANSPLANT MONITORING IN CANADA

McGivern, Adam[1,2] Fenninger, Franz,[1,2] Xu, Rulan[2] Sherwood, Karen[1,2] Keown, Paul[1,2,3] Lan, James[1,2,3]

43 **NINA REECE**
MSc student

EVALUATING THE THERAPEUTIC POTENTIAL OF FUCOIDAN FOR COATING DRUG-ELUTING STENTS

Reece, Nina[1,2], Buenaventura, Gaea[1,2], Chatha, Aakar[1,2], Ho, Vivian[1,2], Elishaev, Maria[1,2], Cheng, Wan-Hei[1,2], Leung, Samuel[1,2], Sun, Tao[1,2], Kong, Hyejin Julia[1,2], Wang, Ying[1,2]

44 **WILLIE WU**
MSc student

DISSECTING TUMOR MICROENVIRONMENT ARCHITECTURE THROUGH SPATIAL ANALYSIS IN EARLY-STAGE NON-SMALL CELL LUNG CANCER

Wu, Willie[1,2]; Anderson, Wyatt[1,3]; Inaba, Fumiya[1,2]; Gallagher, Paul[1]; Noureddine, Kouther[1]; Fitzsimons, Evelyn[1]; Xiang, Richard[4]; Martin, Spencer[3]; McGuire, Anna[4]; Guillaud, Martial[1,2,3]; MacAulay, Calum[1,2,3]; Enfield, Katey[1,2,3]

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MSc student

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MSc student

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MSc student

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Cindy Shi, Majid Alimohammadi

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48 **ISABELLA DIBERARDINO**
MSc student

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49 **CRAIG IVANY**
PhD student

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50 **MICHAEL LANE**
PhD student

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51 **MICHELLE LIN**
PhD student

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52 **ZOE LOFFT**
PhD student

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53 **JOHN PERRIER**
PhD student

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57 **BIANCA RIBEIRO DE SOUZA**

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58 **GENEVIEVE AMARAL**

Resident

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59 **EMMA FINLAYSON-TRICK**

Resident

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60 **REED HUBER**

Resident

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90 **ETHAN KENMUIR**

Graduate Student

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KHASHAYAR HANJANI

Resident

NOBLE 87

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FULL ABSTRACTS

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#1

KRISTEN DANIELLE GO

MSc student · Supervisor: **Dr. Cheryl Wellington**

TITLE

PROTEOMIC ANALYSIS OF BLOOD-BASED NEUROLOGICAL AND INFLAMMATORY BIOMARKERS IN CHRONIC COVID-19

AUTHORS

K. Danielle Go[1,2], Jennifer G. Cooper[1,2], Sophie Stukas[1,2], Ryan L. Hoiland[2], William J, Panenka[2], Mypinder S. Sekhon[2], Nicholas A. Fergusson[3], Noah Silverberg[2], Edward M. Conway[1,4], Thalia S. Field[2,5], William Honer[6,7], A. Jon Stoessl[2], Donna J. Lang[2,6,7], Vesna Sossi[2,6], Cheryl L. Wellington[1,2,8,9]

AFFILIATIONS

[1]Department of Pathology and Laboratory Medicine, University of British Columbia, Vancouver, BC, Canada; [2]Djavad Mowafaghian Center for Brain Health, University of British Columbia, Vancouver, BC, Canada; [3]MD Undergraduate Program, University of British Columbia, Vancouver, BC, Canada; [4]Center for Blood Research, University of British Columbia, Vancouver, BC, Canada; [5]Vancouver Stroke Program, Division of Neurology, Department of Medicine, University of British Columbia, Vancouver, BC, Canada; [6]BC Children's Hospital Research Institute, Vancouver, BC, Canada; [7]BC Mental Health and Substance Use Services Research Institute, Vancouver, BC, Canada; [8]International Collaboration on Repair Discoveries, Vancouver, BC, Canada; [9]School of Biomedical Engineering, University of British Columbia, Vancouver, BC, Canada

ABSTRACT

Background: COVID-19, caused by the SARS-CoV-2 virus, has had almost 800 million reported cases. Most symptoms of acute COVID-19 infection resolve within a few weeks. However, some individuals develop Long-COVID; a condition characterized by symptoms that persist for more than 3 months after the initial infection and commonly includes brain fog. In June 2023, 19.0% of Canadians diagnosed with COVID-19 reported experiencing persisting symptoms. Despite the widespread impact of Long-COVID, its underlying pathology remains poorly understood. This study aims to investigate a diverse panel of neurological and inflammatory blood-based proteins in chronic COVID-19 cases to gain insight into the neuropathology of Long-COVID. We hypothesize that we will identify novel biomarkers associated with clinical outcomes in chronic COVID-19 cases, with a particular focus on their expression in individuals with Long-COVID.

Methods: Plasma samples from 158 unique individuals previously diagnosed with COVID-19 (34.2% male; median age [IQR], 47.5 years [36.0-62.0]) were selected from the British Columbia COVID-19 Consortium Biobank. Biomarker levels were measured using the Alamar NULISAseq™ CNS panel 120 to quantify more than 120 neurological and inflammatory proteins. Participants were classified as having Long-COVID based on self-reported symptoms persisting longer than 2 months. The limma package in R was used to evaluate differential protein abundance of participants with (n=111) and without Long-COVID (n=47). A linear model was fitted for each protein using Long-COVID status as the main predictor and adjusting for age, sex, and other covariates. P-values were adjusted for multiple comparisons using the Benjamini-Hochberg false discovery rate (FDR) method. Principal component analysis (PCA) of all proteins was performed to assess patterns of variation across participants with and without Long-COVID.

Results: Long-COVID participants showed nominally different levels for 6 biomarkers ($p<0.05$) involved in neurodegeneration, inflammation, and growth. However, none of these differences remained significant after FDR correction. Observed fold changes of these biomarkers ranged from 0.9-1.4. PCA revealed that principal component 1 (PC1) explained 28.4% of the variance, and principal component 2 (PC2) explained 11.0%. There was no clear separation between participants with and without Long-COVID along PC1 or PC2.

Conclusion: Our analysis revealed no significant differentially expressed biomarkers between participants with and without Long-COVID. Although several nominally significant proteins were identified, none remained significant after FDR adjustment. Observed effect sizes were small and PCA revealed no clear clustering by Long-COVID status. These findings suggest that plasma proteomic differences associated with Long-COVID are subtle. This potentially reflects Long-COVID heterogeneity due to reliance on self-reporting for diagnosis. Future analyses will look at longitudinal changes of biomarkers using paired samples and explore associations with other clinical measures, such as cognitive scores and imaging data, to clinically stratify Long-COVID participants.

#2

KIDUS ACHALU

PhD student · Supervisor: **Cheryl Wellington**

TITLE

IDENTIFYING BLOOD-BASED BIOMARKERS OF YOUTH SPORTS-RELATED CONCUSSION

AUTHORS

Kidus Achalu BSc[1,2], Jennifer G. Cooper BMLSc[1,2], Jason B. Tabor, PhD[3,4,5], Mohammad Ghodsi BSc[1,2], Tessa Morelli[1,2], Johnny Huang BSc[1,2], Nik Josafatow-García MSc[3,4,5], Linden C. Penner MSc[3,4,5], Sophie, Stukas, PhD[1,2], Jean-Michel Galarneau PhD[3], Douglas D. Fraser MD PhD[6], Jonathan Smirl PhD[3,4,5], Keith Owen Yeates, PhD[4,5,7], Chantel T. Debert MD MSc[3,4,5,8], [#]Carolyn A. Emery PhD[3,4,5,9] and [#]Cheryl L. Wellington PhD[1,2,10]

AFFILIATIONS

[1] Djavad Mowafaghian Centre for Brain Health, University of British Columbia, 2215 Wesbrook Mall, Vancouver, British Columbia, V6T 1Z3 Canada; [2] Department of Pathology and Laboratory Medicine, University of British Columbia, Vancouver, British Columbia, V6T 1Z3 Canada; [3] Sport Injury Prevention Research Centre, Faculty of Kinesiology, University of Calgary, 2500 University Drive NW, Calgary, Alberta, T2N 1N4, Canada; [4] Hotchkiss Brain Institute, University of Calgary, 3330 Hospital Dr NW, Calgary, Alberta, T2N 4N1, Canada; [5] Alberta Children's Hospital Research Institute, University of Calgary, 2500 University Drive NW, Calgary, Alberta, T2N 1N4, Canada; [6] Department of Pediatrics and Clinical Neurological Sciences, Western University, 1151 Richmond Street, London, Ontario, N6A 3K7, Canada; [7] Department of Psychology, University of Calgary, 2500 University Drive NW, Calgary, Alberta, T2N 1N4, Canada; [8] Department of Clinical Neurosciences, Cumming School of Medicine, University of Calgary, 2500 University Drive NW, Calgary, Alberta, T2N 1N4, Canada; [9] Departments of Pediatrics and Community Health Sciences, Cumming School of Medicine, University of Calgary, 2500 University Drive NW, Calgary, Alberta, T2N 1N4, Canada; [1,0] School of Biomedical Engineering, University of British Columbia, 2222 Health Sciences Mall, Vancouver, British Columbia, V6T 1Z3 Canada; [1,1] International Collaboration on Repair Discoveries, University of British Columbia, 818 West 10th Avenue, Vancouver, British Columbia, V6T 1Z3 Canada

ABSTRACT

Background: Sport-related concussions (SRC) are a major health concern, affecting approximately 1 in 10 youth athletes every year. Symptoms following an SRC are often wide-ranging and heterogenous, limiting the reliability of diagnostic methods that are often subjective. Blood-based biomarkers are of interest as they may offer objective, cost-effective, and minimally invasive tools to assist in the diagnosis of SRC. In this study, we employed a targeted discovery approach using Alamar's ultrasensitive NULISA platform to measure 131 unique central nervous system (CNS)-relevant biomarkers. We aimed to identify biomarkers with potential utility as a standalone diagnostic blood test for SRC.

Methods: Paired plasma samples collected preseason and within 10 days following SRC had 131 CNS-related biomarkers quantified utilizing the Alamar platform. Normality was assessed via Shapiro-Wilk; Wilcoxon Signed-Rank test was used for non-normally distributed biomarkers and paired t-test for normally distributed ones. A logistic LASSO mixed effects model was used to identify biomarkers with non-zero coefficients. A Bayesian mixed effects model with a horseshoe prior will also be used to identify biomarkers with diagnostic utility. Biomarkers identified by two or more feature selection methods will be used to build a consensus biomarker panel. The consensus biomarker panel will train a Random Forest classification model to assess the biomarker panel's accuracy, sensitivity, specificity and AUC for classifying SRCs. Model performance will be externally validated in an independent cohort of youth athletes (n=38).

Preliminary Results: In total, 67 paired plasma samples (n=44 males; 65.7%) with a median age [IQR] of 16.45 [15.7 – 17.1] years were analyzed. Of the 131 biomarkers quantified, 7 biomarkers did not meet detectability thresholds and were excluded from analysis. The Wilcoxon Signed-Rank tests and paired t-tests found 50/124 (40.3%) biomarkers that were significantly different (adjusted $p < 0.05$) between pre-injury and post-SRC samples after applying Benjamini-Hochberg correction. A logistic LASSO penalized mixed effects model was fit to classify SRC status (preseason/post-SRC) as the dependent variable. Fixed effects included all 124 biomarkers, age, and body mass index (BMI) and a random intercept was included for each participant to account for repeated measures. The optimal penalty parameter was selected via Bayesian Information Criteria (BIC) across a decreasing grid of λ values (500 to 0), with $\lambda = 15$ minimizing BIC and retaining 5 non-zero fixed-effect coefficients.

Significance/Next Steps: A Bayesian mixed effects model with a horseshoe prior will be implemented to identify biomarkers selected via this method. The consensus biomarker panel will reduce the list of 124 biomarkers to a parsimonious list of 5-15 biomarkers. These shortlisted biomarkers will be assessed for their diagnostic utility using a Random Forest classification model. Identifying a consensus biomarker panel with diagnostic utility for youth SRC could offer an objective blood test reducing reliance on subjective tools.

#3

SINA AZAD

Resident · Supervisor: **Sakara Hutspardol**

NOBLE 88

TITLE

IDENTIFYING SOURCES OF FRICTION IN MASSIVE HEMORRHAGE PROTOCOL MANAGEMENT AT VANCOUVER COASTAL HEALTH: A RETROSPECTIVE MULTICENTRE ANALYSIS OF SAFETY EVENTS AND INCIDENT REPORTING

AUTHORS

Sina Azad[1], Danielle Truong[2], Tara Winckler[2], Caroline Watt[2], Gaby Chan[2], Margaret Roche[2], Lawrence Sham[2], Tyler Smith[1,2], Jacqueline Trudeau[3], Alex Dotto[2,3], Sakara Hutspardol[1,2]

AFFILIATIONS

[1] Department of Pathology and Laboratory Medicine, Faculty of Medicine, UBC; [2] Department of Pathology and Laboratory Medicine, VCH; [3] Department of Anesthesiology, Pharmacology and Therapeutics, UBC

ABSTRACT

Background:

Massive hemorrhage protocols (MHPs) are structured workflows to support the delivery of blood products during severe hemorrhage. MHPs are high acuity events that often result in process errors and friction points which can affect patient care, safety and blood product waste due to miscommunication. The Patient Safety Learning System (PSLS) is an incident reporting platform that is used to capture patient safety events and process failures for follow up and quality improvement. This quality improvement project sought to identify, quantify and analyze the types of errors that were reported through the PSLS system at Vancouver Coastal Health (VCH), the largest Health Authority serving trauma patients in British Columbia, aiming to improve patient safety during the critical bleeding events.

Methods:

A retrospective descriptive analysis was performed by reviewing all PSLS events reported to the Transfusion Medicine (TM) laboratory at VCH sites between January 1, 2023 to December 31, 2024. Each event was manually reviewed, with particular focus on the event description to identify events relevant to MHP activations or emergency blood product requests. Root causes were determined during the review rather than relying on reporter categorization, as existing PSLS categories do not capture MHP specific failure modes. Pareto analysis was applied to the recategorized MHP incidents. A fishbone diagram was used to map root causes across six domains: People, Process, Technology, Environment, Communication, Materials.

Results:

MHPs or emergency blood product use events accounted for 77 (11.8%) of the total 652 PSLS events. A Pareto analysis (80/20 rule) identified Documentation issues at 38 (49.4%) events, Product Handling/Waste at 14 (18.2%) events and Communication/Delivery failure at 11 (14.3%) events, as the main contributing friction points accounting for 81.9% of all MHP events. Ordering/Protocol errors accounted for 8 (10.3%) and Wrong Patient/Identity errors at 6 (7.8%) events. The events are compounded during active resuscitation at the Emergency Department and patient transfers. Ishikawa analysis identified key root causes: absence of a forcing function for documentation return, reliance on paper-based reconciliation in a chaotic resuscitation environment, and tag design that does not facilitate detachment of a reconciliation component.

Conclusions:

Documentation and traceability failures accounted for the largest source of friction in MHP activations, highlighting a systemic process gap in hemovigilance that hinders TM Lab's ability to track emergency product disposition and confirm transfusion to intended recipients. Using a Plan-Do-Study-Act framework, the next steps and recommended approach would be to: (Plan) redesign of the hospital issue tag to include a perforated yellow reconciliation stub that can be detached and returned to TM via collection pouch; (Do) pilot interventions for all MHP activations at VGH; (Study) measure documentation return rates against the baseline failure rate; (Act) adopt, adjust or expand based on outcomes.

#4

WYATT ANDERSON

PhD student · Supervisor: **Dr. Katey Enfield**

NOBLE 73

TITLE

KRAS AND STK11 MUTATIONS SHAPE IMMUNE INFILTRATION AND RESPONSE TO IMMUNOTHERAPY IN NON-SMALL CELL LUNG CANCER

AUTHORS

Anderson, Wyatt[1,2,3]. Liao, Daniella[2,3] . Fong, Arwen[3]. Xiong, Will[1,3]. Fitzsimons, Evelyn[3]. De Souza, Vanessa[1,2,3]. Wu, Willie[2,3]. Enfield, Katey[1,2,3]

AFFILIATIONS

[1]Department of Pathology and Laboratory Medicine, University of British Columbia, Vancouver, B.C., Canada. [2]Department of Basic and Translational Research, BC Cancer Research Institute, Vancouver, B.C., Canada. [3]British Columbia Cancer Research Center, Vancouver, B.C., Canada.

ABSTRACT

Background/Objectives: Lung cancer is the leading cause of cancer deaths worldwide with non-small cell lung cancers (NSCLC) comprising 85% of cases. Immune checkpoint inhibitors (ICI) have improved lung cancer patient outcomes, yet only 20% of patients have durable clinical benefit. The mechanisms underlying ICI resistance are unclear, but understanding could lead to improved personalized treatment or function as biomarkers for treatment success. Previous association studies have linked certain driver mutations, including *KRAS* with *STK11*, with worse ICI outcomes. These mutations are frequently observed in NSCLC adenocarcinoma subtypes (LUAD), but the biology underpinning these observations has yet to be fully resolved. Our objective is to investigate how *KRAS* and *STK11* driver mutations influence the tumour-immune landscape to explore potential mechanisms underlying their association with ICI resistance in NSCLC.

Methods: Publicly available RNA-sequencing (RNA-seq) data (FASTQ and transcripts per million (TPM)) was downloaded from the CodeBreak 100/200 $KRAS^{G12C}$ tumour exclusive clinical trials used to examine the efficacy of the $KRAS^{G12C}$-specific inhibitor sotorasib (n=234), and the LUAD cohort of the Cancer Genome Atlas (TCGA, n=505) with each cohort's mutational metadata. FASTQ files were processed using the TRUST4 pipeline to extract BCR and TCR sequences for repertoire diversity analysis and BCR class frequency. Inverse Simpson (clonal diversity) and ACE scores (clonal richness) were calculated.

Results: We compared 516 curated immune associated genes in $KRAS^{G12C}$ CodeBreak100/200 samples with *STK11* mutations ($STK11^{mut}$) against *STK11* wild-type ($STK11^{wt}$). 87 genes had significantly altered expression with $STK11^{mut}$ tumours compared to $STK11^{wt}$ tumours ($p \leq 0.05$, False Discovery Rate (FDR) ≤ 0.1). Examining similar mutational profiles in the TCGA, there were 31 significantly altered genes. Comparing $STK11^{mut}$ only with $STK11^{wt}$ only tumours resulted in 152 significantly altered genes. There were no significant differences between $KRAS^{wt}/STK11^{mut}$ and $KRAS^{mut}/STK11^{mut}$. In both cohorts, the altered gene expression seen with $STK11^{mut}$ tumours were associated with T cells and immune cell infiltration. Examining lymphocyte receptor metrics in both cohorts, there were no significant differences in the number of unique B cell CDR3 sequences or immunoglobulin class frequencies. In both cohorts, there were significantly fewer unique TCR CDR3 sequences, lower ACE scores, and lower Inverse Simpson scores in $STK11^{mut}$ tumours compared to the $STK11^{wt}$ tumours.

Conclusions: These results indicate that *STK11* mutations are associated with decreased transcriptional signal for T cells and immune cell infiltration, with poorer diversity in the antigen recognition sites of infiltrating T cells. This provides potential mechanistic insight for previously described associations between *KRAS*/*STK11* mutations and poor ICI outcomes. With no significant differences in gene expression profiles between $KRAS^{mut}/STK11^{mut}$ tumours and $KRAS^{wt}/STK11^{mut}$, the findings indicate changes in immune metrics may be an *STK11* dependent phenomenon, which could lend insight into ICI efficacy.

#5

ZHIHAN WANG

PhD student · Supervisor: **Dr. Honglin Luo**

NOBLE 74

TITLE

UNRAVELING THE GENETIC FACTORS INFLUENCING SUSCEPTIBILITY AND RESISTANCE TO VIRAL MYOCARDITIS.

AUTHORS

Zhihan Wang [1,2]; Yasir Mohamud [1,2]; Amrit Singh [1,3]; Tao Sun [1]; Honglin Luo [1,2]

AFFILIATIONS

[1] Centre for Heart Lung Innovation, St Paul's Hospital, Vancouver, BC, Canada; [2] Department of Pathology and Laboratory Medicine, Faculty of Medicine, UBC, Vancouver, BC, Canada; [3] Department of Anesthesiology, Pharmacology and Therapeutics, Faculty of Medicine, UBC, Vancouver, BC, Canada

ABSTRACT

Background/objectives: Myocarditis is an inflammatory disease of the heart, usually caused by viral infections, with enteroviruses being among the most prevalent etiological agents associated with this disease. Between 5-15% of patients with viral infections may develop myocarditis, with 10-20% progressing to dilated cardiomyopathy. Notably, the pathogenesis of viral myocarditis shows a strong sex difference, with the most severe symptoms occurring in males. I have recently conducted a genetic analysis on the GSE35182 Gene Expression Omnibus (GEO) dataset, comparing gene expression in enteroviral myocarditis between male and female mice, by which an exciting novel candidate named circadian associated repressor of transcription (CIART) was identified as a potential contributing factor to the observed sex difference. CIART exhibits unique upregulation in males compared to females and plays a key role in the transcriptional repression of genes involved in regulating circadian rhythms. However, the role of CIART in viral myocarditis has not been explored. This study **aims** to investigate the role and regulation of CIART in viral myocarditis and assess the therapeutic potential of targeting CIART in its treatment. The **hypothesis** is that dysregulation of CIART in males contributes to the pathogenesis of viral myocarditis.

Methods:

We analyzed differential gene expression in 3 normal and 3 CVB3-infected male and female mice at 10 days post-infection from GSE35182 using the “limma” R package. CIART showed the most significant sex-based expression difference between pre- and post-infection. To further test CIART’s function, we will examine its expression in male and female mice with Coxsackievirus B3 (CVB3)-induced myocarditis using CRISPR/Cas9 gene editing and immunohistochemistry, aiming to link CIART levels with disease severity. The research will explore molecular pathways affected by CIART through transcriptomic and proteomic analyses and validate its regulatory role via in vitro models and genetic engineering. Finally, we'll test CIART modulation's therapeutic potential in a cardiac-specific CIART-deficient mouse model, assessing its impact on myocardial inflammation, immune response, and cardiac function.

Results: Our research uncovered a notable difference in CIART expression between males and females following Coxsackievirus B3 (CVB3) infection. Specifically, we observed an upregulation of CIART expression in males (n=3), contrasted with a downregulation in females (n=3). In vitro experiments in cardiomyocyte cell lines, along with immunohistochemistry on heart tissue, further demonstrated CIART mislocalization after CVB3 infection in both sexes. Notably, CIART knockdown in HeLa cells resulted in reduced viral infection.

Conclusions: These initial findings provide a valuable foundation for further exploration into the sex-based differences in susceptibility to CVB3-induced myocarditis. Identifying CIART as a therapeutic target could offer personalized treatment for viral myocarditis, especially in males, and may revolutionize the management of this disease.

#6

CECILIA LEE

MSc student · Supervisor: **Christian Steidl**

NOBLE 66

TITLE

MODELING AND CHARACTERIZATION OF CYTOKINE RECEPTOR COMMON B CHAIN MUTATIONS IN MEDIASTINAL LYMPHOMAS

AUTHORS

Cecilia Lee[1,2], Shinya Rai[3], Gerben Duns[2], Yifan Yin[2], Tomohiro Aoki[4], Grace Cheng[5], Sandra Spencer Miko[5], Gregg Morin[5], David Scott[2], Christian Steidl[2]

AFFILIATIONS

[1]Department of Pathology and Laboratory Medicine, University of British Columbia; [2]Centre for Lymphoid Cancers, BC Cancer Research Institute; [3]Department of Hematology and Rheumatology, Kindai University; [5]Princess Margaret Cancer Centre, University of Toronto; [4]Genome Sciences Centre, BC Cancer Research Institute

ABSTRACT

Background: Mediastinal lymphomas are cancers arising from lymphocytes that occupy the mediastinum, an anatomical site encompassing the thoracic organs and thymus. Two lymphomas that typically manifest in the mediastinum are classic Hodgkin lymphoma (CHL) and primary mediastinal B cell lymphoma (PMBCL) with both cancers showing increased prevalence in adolescent and young adult patients. Relapsed and refractory disease still pose significant challenges to clinical management and toxicities remain an issue, motivating more targeted treatment approaches. We recently identified recurrent, C-terminal truncating mutations in colony stimulating factor 2 receptor subunit beta *(CSF2RB)* in 24% (n=26/107 cases) of CHL and 19% (n=30/153) of PMBCL. *CSF2RB* encodes for a subunit of the beta common cytokine receptor, which activates Janus kinase/signal transducer and activator of transcription (JAK/STAT) and other pathways. However, the mechanisms by which *CSF2RB* mutations drive mediastinal lymphoma pathogenesis remain unclear.

Methods: To generate *CSF2RB* mutants, we used the CRISPR-Cas9 system with custom guide RNAs targeting the *CSF2RB* C-terminus in the PMBCL cell line U-2940. Isogenic clones were obtained through single-cell expansion and truncated mutants were identified with Sanger sequencing. Expression and signaling phenotypes were assessed by flow cytometry (FCM), qPCR, and western blotting following stimulation with interleukin (IL)-5, a beta common cytokine. To investigate the mechanism underlying signaling changes, we transduced FLAG-tagged mutant and wildtype (WT) CSF2RB vectors in the CHL cell line L-428. Immunoprecipitation-mass spectrometry (IP-MS) was performed following FLAG-pulldown and differential binding partners were identified.

Results: Homozygous (n=3) and heterozygous (n=2) U-2940 *CSF2RB*-mutants showed higher surface expression of CSF2RB protein (FCM) compared to WT clones (n=4). Notably, similar transcript levels were observed (qPCR), suggesting increased surface retention of the receptor. *CSF2RB*-mutants also demonstrated stronger activation of STAT5 following 48h stimulation with IL-5. Sustained STAT5 activation was also observed following cytokine withdrawal in the mutant clones, whereas signaling was abolished in the WT clones. IP-MS revealed an overall loss of interacting partners to mutant CSF2RB in the L-428 FLAG model, as expected with the deletion of protein binding domains in the truncated C-terminus. In particular, a differential loss of 3 members of the 14-3-3 family of phosphoserine/threonine adaptor proteins was observed in the mutant cells.

Conclusions: *CSF2RB* mutations in U-2940 upregulate receptor surface expression, which may be due to decreased receptor internalization or degradation. Upregulation of mutant CSF2RB confers stronger and sustained STAT5 activation, contributing to mediastinal lymphoma pathogenesis. The molecular mechanism underlying these changes may be due to a loss of canonical binding partners such as 14-3-3 adaptor proteins, warranting future investigations. In summary, our data uncover a novel, targetable axis in mediastinal lymphoma that can inform better treatment alternatives for patients.

#7

FABIAN FRONTZEK

PhD student · Supervisor: **Christian Steidl**

TITLE

SOMATIC IRF4 MUTATIONS ENHANCE IL10-JAK-STAT3 SIGNALING IN DIFFUSE LARGE B-CELL LYMPHOMA OF THE ABC SUBTYPE

AUTHORS

Fabian Frontzek[1,2], Gerben Duns[1], Michael Li[1], Shinya Rai[1], Rosalie Zhou[2], Jeffrey Niu[1], Jasper Wong[1], Amos Fong[1], Adèle Telenius[1], Claudia Cassidy[1], Laura Hilton[1], David W. Scott[1,2], Christian Steidl[1,2]

AFFILIATIONS

[1]Department for Basic and Translational Research, Lymphoid Cancer Research, BC Cancer, Vancouver, Canada; [2]University of British Colombia, Department of Laboratory Medicine and Pathology, Vancouver Canada

ABSTRACT

Introduction: Diffuse large B-cell lymphoma (DLBCL) is the most common aggressive B-cell lymphoma. Although two thirds of patients are cured with standard immunochemotherapy, outcomes remain poor for those with relapsed or refractory disease. To identify novel therapeutic targets for these patients, we sought to uncover previously unrecognized drivers of disease. One such candidate is the transcription factor *IRF4*, a key regulator of B-cell biology that is recurrently altered by point mutations, amplifications, and structural variants across lymphoid malignancies. In the activated B-cell like (ABC) subtype of DLBCL, mutations affecting the DNA binding domain of *IRF4* occur in ~10% of cases but the functional effects of these mutations remain unclear. We hypothesize that *IRF4* mutations are selected during lymphomagenesis and promote disease-specific transcriptional programs in ABC DLBCL.

Methods: To determine the frequency and hotspots of somatic *IRF4* mutations, we analyzed next-generation sequencing data from archived primary DLBCL samples. Selected *IRF4* hotspot mutations were introduced into two ABC DLBCL cell lines using Prime Editing (PE). Transcriptomic changes in prime-edited isogenic single clones were profiled by RNA-Seq. Differential gene expression analysis (DGEA) was performed using DESeq2, followed by Gene Ontology analysis to identify enriched expression signatures. ATAC-seq was performed to assess differences in chromatin accessibility. Selected pathways were further confirmed at the protein level using Western blotting and ELISA. To validate our findings in primary ABC DLBCL biopsies, we performed DGEA and gene set enrichment analysis (GSEA) on pseudobulk B cells utilizing the spatial transcriptomics platform NanoString CosMx.

Results: In a cohort of 1999 primary DLBCL samples, somatic *IRF4* mutations were detected in 4% of cases (80/1999). Application of the LymphGen classifier revealed an enrichment of *IRF4*mutations in the MCD genetic subgroup (18/194, 9.3%), which predominantly comprises ABC DLBCLs. IRF4pL70V, the most frequently detected IRF4 mutation, and IRF4pS18R occurred in 2.3% and 1.4% of all MCD cases, respectively. To investigate their functional impact, both hotspot mutations were introduced into the ABC DLBCL cell lines HBL-1 and OCI-Ly3 using PE. RNA-Seq analysis of prime-edited isogenic cells revealed enrichment of IL-10-JAK-STAT3-related gene signatures, with *IL10*, *STAT3*, *MCL1*, and *BIRC3* among the most strongly upregulated genes in mutant cells (adj $p<0.001$). ATAC-seq analysis confirmed enhanced accessibility at promoter regions controlling IL10-JAK-STAT3-associated genes. Consistent with these findings, ELISA analysis of cell culture supernatants demonstrated significantly increased IL10 secretion ($p<0.05$, t-test) and Western blot analysis confirmed marked upregulation of phosphorylated STAT3 in mutant cells. Finally, GSEA of 213 primary ABC DLBCL cells using NanoString CosMx revealed a significant upregulation of JAK-STAT3 related signatures in *IRF4* mutant cases (N=42, 20%). Notably, a gene signature comprising the top 30 upregulated genes identified in the *IRF4* mutant cell lines was also significantly enriched in the primary mutant ABC cases (adj $p<0.01$). Cellular composition analysis further revealed significant depletion of $CD4^+$, regulatory, and cycling T cells in IL10-high vs. IL10-low ABC DLBCLs (adj $p< 0.05$).

Conclusions: We provide functional evidence that *IRF4* hotspot mutations are enhancers and modulators of IL10-JAK-STAT3 signaling, a key oncogenic pathway in ABC DLBCL. Further analyses will focus on the altered DNA binding properties of mutant *IRF4* and associated targetable vulnerabilities.

#8

HASAN HAMZE

Resident · Supervisor: **Dr. Victor Yuen**

NOBLE 89

TITLE

REDUCING CARBAPENEM USE FOR LOW-RISK AMPC-PRODUCING ENTEROBACTERALES: IMPACT OF A MICROBIOLOGY COMMENT-BASED QUALITY INITIATIVE.

AUTHORS

Hamze, Hasan[1], Amaral, Genevieve[1], Aloufi, Ahmad[2], Lo, Calvin[1], May, Stephanie[3], Grant, Jennifer [4,5], Yuen, Victor[1,3].

AFFILIATIONS

[1] Department of Pathology and Laboratory Medicine, University of British Columbia, Vancouver, British Columbia, Canada; [2] Antimicrobial Stewardship Program, Providence Health Care, Vancouver, BC, Canada; [3] Department of Pathology and Laboratory Medicine, Royal Jubilee Hospital, Vancouver Island Health, Victoria, BC, Canada; [4] BC Centre for Disease Control, Public Health Laboratory, Vancouver, BC, Canada; [5] Division of Infectious Diseases, University of British Columbia, Vancouver, BC, Canada

ABSTRACT

Background/objectives: AmpC β-lactamases can lead to development of ceftriaxone and piperacillin-tazobactam resistance, even when organisms are initially susceptible in vitro. However, the likelihood of AmpC derepression varies among different Enterobacterales. This study aimed to assess the impact of an AmpC stewardship intervention on the definitive treatment of low-risk Enterobacterales bacteremia.

Methods: This study was a pre-test, post-test quasi-experimental quality study conducted at hospitals in Vancouver Island, Canada. An AmpC stewardship intervention involving the amendment of microbiology report comments regarding ceftriaxone and piperacillin-tazobactam resistance was implemented on February 13, 2023. Adults aged 18 and older who received definitive therapy and had blood cultures growing low-risk organisms (*S. marcescens, P. vulgaris, P. rettgeri, or M. morganii*) were included. The pre-intervention period was from June 2021 to February 2023, and the post-intervention period was from February 2023 to October 2024. The primary endpoint was definitive ceftriaxone or piperacillin-tazobactam therapy. Secondary endpoints examined treatment failure, resistance development, and *Clostridioides difficile* infection.

Results: A total of 56 patients were included: 25 in the pre-intervention group and 31 in the post-intervention group. Definitive ceftriaxone therapy was prescribed less frequently (5%) pre-intervention compared to (44%) post-intervention ($P < 0.001$). After adjusting for critical illness, patients in the post-intervention group were more likely to receive definitive ceftriaxone 17.7 (CI 1.9-162.6). No patients required retreatment, and no ceftriaxone resistance was observed within 30 days in either group. *Clostridioides difficile* infection rates were low in both groups.

Conclusions: This antimicrobial stewardship and laboratory quality intervention led to an increase in ceftriaxone and piperacillin-tazobactam prescribing compared to meropenem for low-risk AmpC-producing Enterobacterales, without affecting patient outcomes and increasing antibiotic resistance rates.

#9

CYRIL HELBLING

PhD student · Supervisor: **Dr. DeMarco**

TITLE

A DIGITAL ALPHA-SYNUCLEIN SEED AMPLIFICATION ASSAY

AUTHORS

Cyril Helbling[1], Mari L. DeMarco[1,2]

AFFILIATIONS

[1]Department of Pathology and Laboratory Medicine, University of British Columbia, Vancouver, Canada; [2]Department of Pathology and Laboratory Medicine, Providence Health Care, Vancouver, Canada

ABSTRACT

Background: Synucleinopathies, including Parkinson's disease, are characterized by the misfolding and aggregation of alpha-synuclein (asyn) in the central and peripheral nervous systems. Due to high rates of misdiagnosis, a biomarker tool is needed to enable early and accurate diagnosis of synucleinopathies. Cerebrospinal fluid (CSF) seed amplification assays (SAA) for detection of asyn pathology have demonstrated high diagnostic accuracy in research settings, but they lack suitability for clinical implementation given their methodological complexity, week-long turnaround times, and high cost per test. To alleviate complexity, time and cost, we developed a microfluidic SAA technique and compared this approach to our previously developed traditional SAA.

Methods: In the traditional SAA approach, samples are run in 96-well plates with detection of thioflavin-T fluorescence on a standard plate reader. For the microfluidic approach, the SAA solution was partitioned into thousands of nanowells with detection at the individual well-level, i.e., digital detection. For the latter, we developed and tested filling solution composition in order to obtain complete and consistent sample partitioning. To assess for sample loading, we analyzed asyn monomers versus fibrils, both with a covalently linked fluorophore. In proof-of-concept studies, we compared the analysis of CSF from persons with and without synucleinopathies (n=10 each) by traditional and microfluidic SAA.

Results: A filling solution was identified that enabled consistent and complete loading of the nanowells, avoiding microfluidic channel clogging. Using the fluorescently labelled asyn monomers and fibrils, both were found to homogenously distributed across the nanowells. For the proof-of-concept experiment using human CSF, synucleinopathies were differentiated from non-synucleinopathies with 100% sensitivity and 100% specificity. The microfluidic approach required 9 uL of reaction volume compare to 400 uL for the traditional approach, and only 1.4 uL of CSF relative to 60 uL for the traditional approach.

Conclusions: Herein we demonstrate the feasibility of a microfluidic approach to asyn SAA. This approach utilizes 40 times less reaction volume than traditional SAA, thus substantially reducing assay reagent cost. It also demonstrates improved analytical sensitivity, which is enabling ongoing investigations into a reduction in analytical time.

#10

KHASHAYAR HANJANI

Resident · Supervisor: **Dr. Anna Lehman**

TITLE

SIMULATING SIGNIFICANCE: COMBINING BIOCHEMICAL TESTING WITH MOLECULAR DYNAMICS SIMULATIONS TO CHARACTERIZE VARIANTS OF UNKNOWN SIGNIFICANCE IN AN UNUSUAL CASE OF DOLICHOL KINASE DEFICIENCY

AUTHORS

Théberge, Emilie[1], **Hanjani, Khashayar[2]**, Monaghan, Jennifer[3], Rakic, Bojana[2], Sinclair, Graham[2], He, Miao[4], Roston, Thomas[5], Hawkins, Nathaniel[5], Lehman, Anna[1]

AFFILIATIONS

[1] Department of Medical Genetics, University of British Columbia (UBC); [2] Department of Pathology and Laboratory Medicine, UBC; [3] Unaffiliated; [4] Department of Pathology and Laboratory Medicine, University of Pennsylvania; [5] Department of Medicine, Division of Cardiology, UBC

ABSTRACT

Background/objectives:

The dolichol kinase gene (*DOLK*) encodes an enzyme required in post-translational protein glycosylation. Autosomal recessive inheritance of biallelic deleterious *DOLK* variants have been associated with a clinical spectrum from isolated pediatric nonischemic cardiomyopathy (NICM) to syndromic forms involving ichthyosis and other organ systems. Herein we present the latest-onset case reported to date of a female presenting at age 43 with a cryptogenic stroke and subsequently identified NICM. Two previously unreported variants of uncertain significance were identified in *DOLK* from cardiomyopathy panel genome sequencing. One variant results in a single amino acid change, while the other extends the protein by disrupting the canonical stop codon. We sought to explore how these changes in protein structure could lead to disease.

Methods:

To phenotype the variants of unknown significance, patient history, diagnostics, and histology were reviewed. Specialized biochemical testing of glycosylation was pursued including transferrin isoelectric focussing and plasma N-glycan analysis.

To further assess the impact of the mutations on the dolichol kinase protein, the structure of each variant protein was modeled using Alpha Fold 3. The predicted structures were subsequently modelled embedded in the endoplasmic reticulum using the PPM 3.0 web server and CHARMM-GUI. Molecular dynamics were simulated using the GROMACS python package.

Results:

Biochemical analyses identified a slightly elevated mono/di-glycosylation ratio, an elevated asialo/di-glycosylation ratio, and significant increases of Man3, Man4 and Man5GlcNAc2 glycans with a markedly increased Man5/9 ratio. Molecular dynamics simulations are currently ongoing.

Conclusions:

Biochemical phenotyping supported the combined pathogenicity of the *DOLK* variants identified as underlying our proband's isolated NICM. The relative mildness in certain abnormalities points to higher residual function compared to typical pathogenic mutations of *DOLK* and could explain the relative late age of symptom onset. Meanwhile, the increasing availability of computational power and accessibility of software now affords opportunities to better conceptualize the bridge between genotype and phenotype.

#11

ZESHUO LI

PhD student · Supervisor: **Helene Cote**

NOBLE 75

TITLE

INFLUENCE OF DNA EXTRACTION METHODS ON THE PREVALENCE OF LOW-FREQUENCY G>A MUTATIONS IN MITOCHONDRIAL DNA

AUTHORS

Zeshuo E.S. Li[1,2], Hailey Chapman[1], Rachel Dunn[1], Loïc C. Caloren[1], Izabelle Gadawska[1], Maria S. Peñaherrera[3,4], Chelsea Elwood[5], Deborah M. Money[5,6], Wendy P. Robinson[3,4], Hélène C.F. Côté[1,2,6,7]

AFFILIATIONS

[1] Department of Pathology & Laboratory Medicine, University of British Columbia, Vancouver, BC, Canada.; [2] Centre for Blood Research, University of British Columbia, Vancouver, BC, Canada,; [3] Department of Medical Genetics, Faculty of Medicine, University of British Columbia, Vancouver, British Columbia, Canada; [4] British Columbia Children's Hospital Research Institute (BCCHR), Vancouver, British Columbia, Canada; [5] Department of Obstetrics & Gynaecology, University of British Columbia, Vancouver, British Columbia, Canada; [6] Women's Health Research Institute, Vancouver, British Columbia, Canada; [7] Edwin S.H. Leong Healthy Aging Program, University of British Columbia, Vancouver, British Columbia, Canada

ABSTRACT

Background:Low-frequency mitochondrial DNA (mtDNA) mutations are increasingly studied in aging, mitochondrial disease, and cancer, where they can inform mutation accumulation, replication fidelity, oxidative damage, and clonal expansion dynamics. However, low-frequency artefactual mutations introduced during upstream sample preparation, such as DNA extraction, can be difficult to distinguish from true biological signals in downstream bioinformatic interpretation. After observing differences in low-frequency mtDNA mutation profiles between samples extracted using Qiagen silica column-based and classical salting-out methods, we systematically evaluated the influence of DNA extraction methods on artefactual mutation signals.

Method:DNA was extracted from human placental specimens (n = 39) and peripheral blood mononuclear cells (PBMCs; n = 6) using either a Qiagen silica column-based method or a classical salting-out method. Low-frequency mutations were quantified using URMD-Seq, a molecular barcoding-based approach for accurate and scalable detection of ultra-rare mutations in the mtDNA control region. For downstream analysis, somatic low-frequency mutations were defined as variants with a variant allele frequency < 2%. Additional experiments were performed in a random subset of placental specimens to investigate sources of the observed artefactual signals, including gel electrophoresis using extracted commercial DNA ladders to assess DNA fragment size recovery, a salt exposure time course to test the effect of prolonged incubation in high-salt buffer, lysis buffer swapping to isolate the contribution of lysis chemistry, and cross-extraction to determine whether artefactual signals persist after re-extraction with the alternative protocol.

Results:Compared with the Qiagen method, the salting-out method showed an increased prevalence of G>A mutations with low frequency in both placental specimens ($P < 0.0001$) and PBMCs ($P < 0.05$). Gel electrophoresis analysis showed that DNA extracted using the Qiagen method retained longer fragments but showed reduced recovery of shorter fragments, whereas DNA extracted using the salting-out method more closely resembled untreated controls in fragment size distribution. However, cross-extraction experiments showed that the G>A mutation signal did not change significantly after re-extraction with the alternative protocol ($P = 0.19$), supporting that this signal is not selectively lost by Qiagen. Increasing incubation time in high-salt buffer was not significantly associated with increased G>A artefacts (chi-square = 4.39; $P = 0.62$). Lysis buffer swapping supported a role for the salting-out lysis buffer chemistry in the observed mutation pattern ($P < 0.05$).

Conclusions:DNA extraction methods can influence the prevalence of artefactual low-frequency G>A mutations detected in mtDNA. Our findings support a role for extraction-associated lysis chemistry in shaping this mutation pattern and identify DNA extraction as an important pre-analytical variable in rare mtDNA mutation studies. DNA extraction protocols should therefore be carefully considered and fully disclosed when interpreting low-frequency mtDNA variants.

#12

ABBEY SUGARS-KEEN

MSc student · Supervisor: **Dr. Ed Conway**

TITLE

NEW INSIGHTS INTO THE THROMBOTIC COMPLICATIONS OF TYPE 2 DIABETES

AUTHORS

Abbey Sugars-Keen[1], Paniz Ghavimi[1], Nooshin Safikhan[1], Kevin Gonzalez[1], Nathanael Caveney[2], Edward Conway[1]

AFFILIATIONS

[1] Centre for Blood Research, University of British Columbia; [2] Department of Pharmacology and Toxicology, University of Toronto

ABSTRACT

Background/objectives: Type 2 diabetes (T2D) is a global health crisis, causing over 3 million deaths per year. Acquired later in life due to factors such as genetics, physical activity, and diet, T2D is characterized by the development of insulin resistance in adipose (fat), skeletal muscle, and liver. The disruption of insulin-dependent signaling results in chronically heightened circulating blood glucose levels. T2D is strongly linked to vasculothrombotic diseases, which account for 80% of deaths among patients. Unfortunately, the mechanistic links between thrombosis (pathological blood clotting) and insulin signaling remain poorly understood, hindering the development of effective therapies. Work in our lab revealed a direct binding interaction between tissue factor (TF), the major trigger of clotting, and the insulin receptor (IR), the mediator of insulin signaling. We **hypothesize** that **the interaction between TF and the IR allows for functional crosstalk between the glucometabolic and coagulant pathways**, contributing to both the development of insulin resistance and the high rates of thrombosis observed in patients with T2D. In this study, we **aim** to **quantify the kinetics of this interaction and to assess the functional impact on each protein's activity.**

Methods: The TF-IR binding interaction was shown using proximity ligation assays to detect cell surface protein colocalization and microscale thermophoresis to estimate the dissociation constant (Kd). Factor Xa generation assays were performed on human melanoma A7-TF cells (expressing high levels of both proteins) to measure the procoagulant activity of TF in the presence or absence of an anti-IR antibody. Glucose uptake assays were performed on mature adipocytes from wild type mice in the presence or absence of an anti-TF antibody to study the glucometabolic activity of the IR. In a preliminary *in vivo* experiment, mice were placed on a high fat diet for two weeks and injected with an anti-TF antibody. Glucose tolerance tests were conducted, and the weights of several fat depots and tissues were collected.

Results: The binding assays showed that TF and the IR colocalize on the cell surface and bind in purified form with a Kd of 61±23 nM. Blocking this interaction with anti-IR antibodies significantly increased TF's procoagulant activity. Similarly, treatment of adipocytes with an anti-TF antibody significantly increased glucose uptake in response to insulin. Finally, the mice injected with an anti-TF antibody showed improved glucose tolerance and lower weight gain in two fat depots following two weeks on high fat diet.

Conclusions: These results suggest that the interaction between TF and the IR is mutually inhibitory and implicates TF in *in vivo* glucometabolism. This novel interaction could open new avenues for therapeutic development. Since thrombotic complications represent the most common cause of death among patients with T2D, effective treatments are urgently needed.

#13

JHUNAM SIDHU

PhD student · Supervisor: **Dr. David Granville**

TITLE

DEGRADOMIC ANALYSIS REVEALS NOVEL ROLE FOR GRANZYME K IN INFLAMMATION AND PSORIASIS

AUTHORS

Jhunam Sidhu[1,2,3], Katlyn L. Richardson[1,2,3], Anna Prudova[1,2,3], Alexandre Aubert[1,2,3], David J. Granville[1,2,3]

AFFILIATIONS

[1]International Collaboration on Repair Discoveries (ICORD) Centre, Vancouver Coastal Health Research Institute, University of British Columbia, Vancouver, BC, Canada; [2]Department of Pathology and Laboratory Medicine, University of British Columbia, Vancouver, BC, Canada; [3]British Columbia Professional Fire Fighters' Burn and Wound Healing Group, Vancouver Coastal Health Research Institute, University of British Columbia, Vancouver, BC, Canada

ABSTRACT

Background/objectives:

Psoriasis is a chronic autoimmune skin disease characterized by persistent inflammation, keratinocyte hyperproliferation, and thickened plaques, affecting ~3% of the global population. Inflammation in psoriasis is driven by complex interactions between epithelial and immune cells, with serine proteases emerging as key regulators. Granzyme K (GzmK) is a trypsin-like protease belonging to the granzyme family of serine proteases. GzmK is elevated in human psoriatic skin, drives keratinocyte proliferation, and promotes inflammation in part through the secretion of IL-23 by immune cells. Furthermore, GzmK deficiency significantly reduced disease severity in a mouse model of psoriasis. In the present study, a degradomic approach was utilized to identify novel GzmK substrates. Among candidate substrates revealed, Glycoprotein Non-Metastatic Melanoma Protein B (GPNMB), a type I transmembrane protein that is suggested to function as a negative regulator of inflammation was identified. GPNMB modulates intracellular signaling pathways, including decreasing pro-inflammatory cytokine expression, and promotes macrophage polarization toward an anti-inflammatory M2 phenotype. We hypothesized that GzmK cleaves GPNMB, thereby altering its immunomodulatory function and promoting inflammatory pathways.

Methods:

In the present study, a non-biased degradomic approach was utilized to identify novel GzmK substrates. Human keratinocytes were treated with recombinant GzmK and supernatants were collected and subjected to N-terminomic analysis TAILS (Terminal Amine Isotopic Labeling of Substrates). TAILS is a mass-spectrometry-based approach that identifies and quantifies all neo-N-termini resulting from the introduction of GzmK. From the novel substrates identified, GzmK cleavage was validated using western blot analysis of recombinant protein incubated with GzmK, as well as in keratinocytes following GzmK treatment.

Results:

TAILS analysis revealed increased abundance of GPNMB-derived cleavage fragments in the presence of GzmK, indicating proteolytic processing. Consistently, western blot analysis confirmed direct cleavage of recombinant GPNMB by GzmK in a cell-free cleavage assay and demonstrated cleavage of endogenous GPNMB in keratinocytes upon GzmK treatment in vitro.

Conclusions:

Disruption of GPNMB-mediated anti-inflammatory signaling by GzmK-dependent cleavage may promote inflammatory responses in conditions such as psoriasis. Ongoing studies are focused on defining the functional consequences of GPNMB cleavage on immune signaling and macrophage polarization.

#14

OPEYEMI PELUOLA

Resident · Supervisor: **Dr. Julia Naso**

TITLE

MOLECULAR FEATURES ASSOCIATED WITH TUMOR BUDDING AND RECURRENCE IN LUNG SQUAMOUS CELL CARCINOMA

AUTHORS

Opeyemi Peluola,[1] Cathy Yan,[2] Richard Corbett[2], Melanie Bailey[2], Zhou Fang,[3] Drew Smith,[1] Jennifer Ji,[1] Marco Marra[4,5], Julia Naso[1,6]

AFFILIATIONS

[1] Department of Pathology and Laboratory Medicine, University of British Columbia; [2] Michael Smith Laboratories, University of British Columbia; [3] Undergraduate Medicine, University of British Columbia; [4] Department of Medical Genetics and Michael Smith Laboratories, University of British Columbia; [5] BC Cancer Research Institute, BC Cancer; [6] Department of Pathology and Laboratory Medicine, Vancouver General Hospital

ABSTRACT

Background/objectives: Lung squamous cell carcinoma (LUSC) has high recurrence rates even after curative intent surgery. High grade tumor budding is associated with increased recurrence risk of LUSC. A tumor bud is defined as a single cell or a group of four or less cells surrounded by stroma at the border of a tumor. The objective of this study was to understand the molecular contexts in which tumor budding occurs, and to identify factors that may make a tumor prone to high grade budding. We studied this by evaluating gene expression in bulk and single cell datasets.

Methods: Deep whole genome sequencing on resected primary tumor and matched normal archival clinical formalin fixed tissue was performed for 71 LUSC tumors. Retrospective recurrence outcome data was compiled from clinical charts. Tumors were scored for tumor budding on the H&E-stained slide of the representative block used for sequencing. Tumor bud score, the highest number of tumor buds in a 20x field at the edge of the tumor, was categorized as low (0-9 buds) or high grade (≥ 10 buds). Bulk RNA sequencing was successful for 47 of the LUSC tumors that had genome sequencing. We also performed 10X Genomic Flex single cell profiling on 26 LUSC tumors from 13 patients in the genome sequencing cohort (2 tumors per patient).

Results: Analysis of carcinoma cells in the single cell gene expression data found 10 genes with significantly higher expression in the high grade tumor budding group (adj. $P < 0.05$): *NDRG2, SPARC, SPON2, MT1E, AEBP1, SLC25A17, THBS2, MAGEA12, CSAG1* and *ETV2*. These genes have functions related to epithelial mesenchymal transition, transcriptional regulation, genome stability, and immune modulation. T-cell subtyping using the single cell profiling data revealed that tumors with high grade budding had lower proportions of activated CD8 T-cells and higher proportions of naïve CD8 T-cells, compared to tumors with low grade budding. In bulk RNAseq data, among the top four genes whose expression correlated with tumor budding scores two were genes known to be associated with lung cancer prognosis, *DAP3* and *PRDX4*, with most variability in the 0-5 budding score range (correlations not statistically significant after multiple test correction). *MUC5B* and *CMYA5* nonsynonymous somatic mutations tended to be associated with recurrence (unadj. $P<0.03$ and 0.04) but were not enriched in the high grade tumor budding group, nor were mutations of other genes.

Conclusions: The tumor microenvironment may play a role in limiting tumor spread through immune-mediated reduction of tumor budding. Differential carcinoma cell gene expression identifies epithelial mesenchymal transition, transcriptional regulation and genome stability as additional features that may predispose some tumor to developing regions of high grade tumor budding.

#15

ALEXANDRA WITT

PhD student · Supervisor: **Ed Pryzdial**

TITLE

IT TAKES TWO: ADJUNCT FACTOR X FOR SAFER CLOT LYSIS

AUTHORS

Witt, Alexandra[1,2,3], Hao, Lihua[2,3], Pryzdial, Ed[1,2,3]

AFFILIATIONS

[1]Department of Pathology and Laboratory Medicine, University of British Columbia; [2]Centre for Blood Research, UBC; [3]Canadian Blood Services

ABSTRACT

Background/objectives: Heart attacks and strokes are the leading causes of death worldwide, most often caused by clots that block the flow of blood. The favoured thrombolytic drug is a recombinant (r) version of tissue plasminogen activator (tPA), however the high rtPA dose required for clot lysis causes hemorrhage in up to 7% of patients, resulting in part from systemic, rather than clot-localized, enzyme activity. Our lab has discovered a thrombolytic function for the plasma protein, clotting factor X (FX), which acts non-enzymatically to accelerate tPA. Here we present a recombinant variant of FX (rFXic) with two key characteristics: an inhibitory (i) mutation that blocks the intrinsic clotting function, and a cleavage-resistant (c) mutation for increased half-life of tPA-accelerating function in plasma. We hypothesize that **rFXic is thrombolytic with superior safety compared to rtPA.**

Methods: The plasmin cleavage profile and prothrombin clotting time of rFXic confirmed the successful insertion of mutations compared to wild type (rFXwt). Acceleration of rtPA activity was evaluated using a plasmin-selective chromogenic substrate. In a mouse model of carotid artery occlusion, Doppler ultrasound recordings of blood flow were used to measure the ability of rFXic to affect clot dissolution. Plasma from mice was evaluated via immunoblot for biomarkers of systemic lysis.

Results: *In vitro*, rtPA generated 10-fold more plasmin in the presence of rFXic than rFXwt, indicative of thrombolytic acceleration by the former. In mouse models of thrombosis, rFXic decreased the thrombolytic dose of rtPA by at least 75% as an adjunctive therapeutic but did not promote thrombolysis without rtPA. Preliminary safety studies showed that fibrinogen degradation products (FDP) and plasmin, biomarkers of systemic lysis, were markedly reduced in mice receiving rFXic as an adjunct therapy.

Conclusions: These data suggest that by lowering the dose of rtPA, rFXic may be used as an adjunct therapeutic to reduce the bleeding risk associated with thrombolysis. With non-inferior efficacy and superior safety as a thrombolytic regimen when compared to rtPA alone, future studies anticipate advocating for rFXic as a safe and effective thrombolytic.

#16

MARK TRINDER

Resident · Supervisor: **Dr. Julia Naso**

TITLE

IMMUNE REGULATORY GENE EXPRESSION PROFILING OF BRONCHOALVEOLAR LAVAGE SPECIMENS FOR DISTINCTION OF LUNG ADENOCARCINOMA FROM BENIGN LESIONS

AUTHORS

Trinder, Mark[1], Wang, Peiyao[2], Lim, Emilia[3], Lockwood, Will[1,2], Naso, Julia R.[1,4]

AFFILIATIONS

[1]Department of Pathology and Laboratory Medicine, University of British Columbia, Vancouver, BC, Canada.; [2]Department of Integrative Oncology, British Columbia Cancer Research Institute, Vancouver, BC, Canada.; [3]Department of Biochemistry and Molecular Biology, University of British Columbia, Vancouver, BC, Canada.; [4]Department of Pathology and Laboratory Medicine, Vancouver General Hospital, Vancouver, BC, Canada.

ABSTRACT

Background/Objectives: Bronchoalveolar lavage (BAL) is a minimally invasive technique that is commonly used to obtain a cytologic diagnosis of malignancy for patients found to have an abnormal lung nodule by medical imaging. However, these specimens often sample the peri-lesional inflammatory environment without capturing any malignant cells. We hypothesized that assessing the gene expression of this inflammatory environment could help discriminate samples as being malignant or benign and reduce the need for further invasive testing.

Methods: This retrospective study included BAL specimens reported as negative for definite malignant cells. After additional sampling or 2 years of imaging follow-up patients were classified as having adenocarcinoma (n=13) or a benign nodule (n=11). RNA was extracted from formalin-fixed paraffin-embedded BAL cell blocks and expression was quantified by nanoString using the nCounter PanCancer Immune Profiling Panel (770 genes).

Results: Gene set enrichment analyses based on KEGG/GO terms found that pathways such as T-cell receptor signaling, PD-L1 expression/PD-1 checkpoint, and alpha-beta T cell activation were significantly down-regulated for adenocarcinoma cases relative to benign controls (q-values<0.05). A gene expression signature of ICAM2, C3, CARD9, TGFB2, PNMA1, and IL22RA2 was able to discriminate adenocarcinoma cases from benign controls with 100% sensitivity and 100% specificity. This finding was reproduced with 100% sensitivity and 100% specificity using an external transcriptomic microarray dataset of BAL specimens (malignant n=9; benign n=6; Kuo et al. 2018).

Conclusion: Gene expression profiling of BAL specimens shows promise for distinguishing malignant from benign pulmonary lesions in limited cytology specimens where no malignant cells are identified.

#17

JENNY ZHAO

PhD student · Supervisor: **Leandro Venturutti**

NOBLE 76

TITLE

TMEM30A LOSS OF FUNCTION MUTATIONS IN B-CELL LYMPHOMA DIFFERENTIALLY IMPACT B CELL SUBSETS AND THEIR FUNCTIONALITIES

AUTHORS

Zhao, Jenny[1, 2, 3], Cardoso, Miguel[1, 3], Pijpers, Lizzy[1, 3], Tang, Jing[1, 3, 4], Nawaz, Waqas[1, 3], Venturutti, Leandro[1, 2, 3]

AFFILIATIONS

[1]Centre for Lymphoid Cancer, British Columbia Cancer, Vancouver, BC V5Z 1L3, Canada; [2]Department of Pathology and Laboratory Medicine, The University of British Columbia, Vancouver, BC V6T 2B5, Canada; [3]Terry Fox Laboratory, British Columbia Cancer, Vancouver, BC V5Z 1L3, Canada; [4]Interdisciplinary Oncology Program, The University of British Columbia, Vancouver, BC V6T 2B5, Canada

ABSTRACT

Background: Diffuse large B cell lymphoma (DLBCL) is a highly heterogeneous disease. However, most patients still receive the same chemo-immunotherapy treatment, which likely explains why ~40% of them experience refractory responses or relapses. While some DLBCL subtypes have been extensively studied, others, such as the BN2 subtype, remains elusive in terms of its origins and biology. Recent studies found that loss-of-function (LOF) mutations in *TMEM30A*, a gene encoding a subunit of the membrane transporter that translocates phosphatidylserine (PS) towards the interior of the cell, are recurrent in BN2 tumours. In the event of TMEM30A loss, PS is exposed on the plasma membrane. Interestingly, a similar phenotype is characteristic of dying cells, flagging them for removal by macrophages that bear PS-binding receptors. As such, the selection of *TMEM30A* LOF mutations by BN2 tumours is unusual in the context of cancer and may suggest a selective advantage. To date, most DLBCL are thought to originate from follicular B cells (FOB). In lymphoid tissue, macrophages are abundant in specialized areas called “follicles”, housing FOBs. Residing outside the follicle are B cells with differing biology called marginal zone B cells (MZB). Surface PS levels at rest in MZB is unusually high, suggesting that this feature may not be detrimental, but confer advantages. We **hypothesize** that TMEM30A loss leads to deleterious effects in FOB, but provide MZB a competitive advantage and illustrate an alternative transformation trajectory in BN2 DLBCL from MZB.

Methods: In transgenic mouse models that allow for the conditional deletion of *Tmem30a* in different B cells subsets, we performed immunization experiments to activate FOB and MZB. At the peak of the FOB and MZB-driven immune responses, we isolated splenocytes to probe cellular activation and signaling status using flow cytometry and collected serum to assess the antibody amount/affinity using ELISA. We then expanded our efforts in profiling MZB surface immune markers with a flow cytometry-based cell surface screen.

Results: Upon immunization in activating FOB to become germinal centre B cells (GCB), we found that *Tmem30a*-KO mice exhibited a 88% reduction in GCB proportions at the peak of the immune response. Analysis from mouse sera further showed a significant decrease of GC-derived antigen-specific antibody amount. Following immunization to activate MZB, we found an 80-100% increase in the display of surface activation markers in *Tmem30a*-KO compared to -CTRL MZB. E*x vivo* stimulation of spleen cells also showed that *Tmem30a*-KO MZB exhibited higher sensitivity stimulation. Furthermore, our screen identified additional activation markers increased in *Tmem30a*-KO MZB, as well as markers that facilitate crosstalk with other immune cells.

Conclusion: Our findings support a model where MZB, instead of FOB, would thrive with TMEM30A loss, a phenotype of BN2 DLBCL, potentially suggesting a transformation trajectory from MZB to BN2 DLBCL. Since DLBCL is generally thought to develop from FOBs, our study may uncover biological insights for developing novel therapeutics/diagnostics to improve patient outcomes.

#18

LYNNE ALTOW

Medical Student · Supervisor: **Dr. Diana N. Ionescu**

NOBLE 79

TITLE

UNDER THE MICROSCOPE: STUDENT PERCEPTIONS OF PATHOLOGY PRACTICE, CAREER, AND CURRICULUM

AUTHORS

Altow, Lynne1, Povshedna, Tetiana[2], Zhao, Michael[1], Hopkins, Jade[1], Ionescu, Diana N.[2,3]

AFFILIATIONS

[1] Faculty of Medicine, University of British Columbia; [2] Department of Pathology and Laboratory Medicine, University of British Columbia; [3] BC Cancer

ABSTRACT

Background/objectives: A persistent global shortage of pathologists is impacting timely diagnosis and patient care. Limited exposure to pathology during undergraduate medical education may contribute to low recruitment. This study examines medical student awareness and perceptions of pathology at the University of British Columbia (UBC), with implications for workforce planning and curriculum design.

Methods: A cross-sectional Qualtrics survey was distributed to UBC medical students (n=103). The survey included multiple-choice, 0–10 Likert-scale, and open-ended questions exploring awareness of pathology careers, understanding of the pathologist's role, familiarity with subspecialties, prior exposure, perceived curricular visibility, and career interest. Participants were stratified by training level: year 1 (Y1, n=37), year 2 (Y2, n=42), and clinical years 3/4 (Y3/4, n=22). Descriptive statistics were used for analysis.

Results: Most Y1 (89%) and Y2 (93%) students, and 45% of Y3/4 students, reported they were still exploring career options. However, few students expressed interest in pathology (Y1: 5%, Y2: 17%, Y3/4: 5%). Awareness of direct-entry pathology specialties increased with clinical training (Y1: 58%, Y2: 49%, Y3/4: 70%). Across cohorts, students reported moderate understanding of the pathologist's role in clinical care (median 6/10), but limited insight into daily practice (median 4/10). Senior students perceived pathology as more "invisible" within the curriculum (median 6.5/10 vs. 5/10).

Conclusions: Pathology remains underrepresented in undergraduate medical education despite its central role in patient care. Early, structured exposure—through mentorship, integrated learning, and clinical experiences—may improve understanding and support recruitment into this essential specialty.

#19

TEJVEER ATWAL

Medical Student · Supervisor: **Dr. Julia Naso**

TITLE

GENOME AND TRANSCRIPTOME SEQUENCING IN NON-SMALL CELL LUNG CANCER IDENTIFIES THERAPEUTIC OPTIONS BEYOND STANDARD OF CARE

AUTHORS

Atwal, Tejveer[1], McConechy, Melissa[2], Csizmok, Veronika[2], Corbett, Richard[3], Chand, Damini[2], Nelson, Jessica[2], Laskin, Janessa[4], Marra, Marco[5,6], Naso, Julia[7,8]

AFFILIATIONS

[1] Undergraduate Medicine, University of British Columbia; [2] Canada's Michael Smith Genome Sciences Centre, Provincial Health Services Authority; [3] Michael Smith Laboratories, University of British Columbia; [4] Division of Medical Oncology, BC Cancer and University of British Columbia; [5] Department of Medical Genetics and Michael Smith Laboratories, University of British Columbia; [6] BC Cancer Research Institute, Provincial Health Services Authority; [7] Department of Pathology and Laboratory Medicine, University of British Columbia; [8] Department of Pathology and Laboratory Medicine, Vancouver General Hospital

ABSTRACT

Background/objectives:

The Personalized OncoGenomics (POG) program performs whole genome and transcriptome sequencing for advanced stage cancers, with patients undergoing review by a multidisciplinary team to discuss individualized treatment options. POG is a pan-cancer project and includes non-small cell lung cancer (NSCLC), which is a heterogeneous and aggressive malignancy in need of novel therapies. We aimed to determine the prevalence of therapeutically targetable alterations and POG-informed therapies among NSCLC POG patients.

Methods:

All non-squamous NSCLC samples profiled by POG between 2013 and 2025 were included. Data were compiled from the POG integrated pipeline reports. All variants listed in the 'Key Genomic and Transcriptomic Alterations' or 'Knowledgebase Matches' sections were used for analysis and input into the current POG knowledgebase to generate updated matches with possible therapies, stratified by IPR evidence level (level A or B indicating evidence from professional guidelines, FDA-approved therapies or well-powered clinical studies, with expert consensus). Homologous recombination deficiency (HRD) was predicted based on HRDetect score > 0.7.

Results:

The POG study profiled 85 non-squamous NSCLCs, of which 69 were adenocarcinoma, 3 were sarcomatoid carcinoma, and 13 were NSCLC not otherwise specified. Median patient age was 60 years and 60% of patients were female. Tumor samples used for sequencing were from metastatic sites (48%), primary tumors (39%) or unspecified sites (13%). Nine (16%) out of 57 patients with TMB data had high-TMB (>= 10 mut/Mb). Five (6%) out of 83 patients with HRDetect scores were considered to be HRD, four of whom had germline or somatic mutations detected in HR-associated genes. The most prevalent gene expression outliers were of *XIAP* (28%), *ARFGEF3* (28%), *EGFR* (27%) and *KAT6B* (27%); the most common amplification was *MYC* (21%) and the most common deep deletion was in *CDKN2A/B* (14%). POG-informed therapy was received by 29 (38%) out of 76 patients with available data. The POG-informed therapies included 12 different tyrosine kinase inhibitors and 3 types of immune checkpoint inhibitors, as well as bevacizumab, BMS-986115 (a gamma secretase inhibitor), everolimus, irbesartan, palbociclib, and trastuzumab. Fifty potential targeted therapeutic agents with the highest IPR evidence levels (A or B) matched to alterations in the cohort. Four patients had possible alternate diagnoses (sarcoma, pancreatic/intestinal adenocarcinoma or neuroendocrine neoplasm) raised by the POG analysis.

Conclusions:

Whole genome and transcriptome sequencing identifies alterations in NSCLC beyond those that would be identified in standard of care testing, many of which have evidence for therapeutic actionability. Determining the prevalence of potentially actionable alterations in NSCLC beyond those on standard clinical panels helps define the added value of comprehensive molecular profiling for NSCLC and identifies high yield targets for inclusion in future clinical testing panels.

#20

POLINA NOVOSELTSEVA

Medical Student · Supervisor: **Dr. Eugene Y. H. Yeung, Dr. Romina Reyes**

NOBLE 80

TITLE

DRUGS VERSUS BUGS: CUMULATIVE ANTIMICROBIAL SUSCEPTIBILITY TESTING OF COMMUNITY-ACQUIRED BLOODSTREAM INFECTIONS IN BRITISH COLUMBIA

AUTHORS

Polina Novoseltseva,[1] Romina Reyes,[1,2] and Dr. Eugene Y. H. Yeung [1,2,3,4]

AFFILIATIONS

[1] Faculty of Medicine, University of British Columbia, Vancouver, B.C., Canada; [2] LifeLabs, Department of Medical Microbiology, Vancouver, B.C., Canada; [3] Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, B.C., Canada; [4] School of Medicine, Simon Fraser University, Surrey, B.C., Canada

ABSTRACT

Background/objectives: Bloodstream infections are a significant cause of community morbidity and mortality, and their microbiological patterns may vary by region. In British Columbia, the Lower Mainland and Vancouver Island represent two major population centres with distinct demographics and exposure profiles. Analysis of community blood culture data provides an opportunity to identify geographic differences in bloodstream pathogens and monitor regional antimicrobial resistance trends over time.

Methods: Blood culture data collected by LifeLabs British Columbia from 2020 to 2024 were analyzed, encompassing 744 community isolates: 620 from the Lower Mainland and 124 from Vancouver Island. Organisms were identified, and antimicrobial susceptibility results were compared between the two regions to assess regional variation in bloodstream infection patterns.

Results: Of all isolates, 62% were Gram-positive and 37% were Gram-negative; yeast accounted for the remaining 1%. In the Lower Mainland, *Salmonella* species (41%) and *Escherichia coli* (32%) were the predominant Gram-negative organisms, whereas *Escherichia coli* (35%) was the most common Gram-negative organism on Vancouver Island. Overall, viridans group *Streptococcus* (22%) and *Staphylococcus aureus* (11%) were the most frequently isolated Gram-positive organisms. *Salmonella* species and *Escherichia coli* demonstrated reduced susceptibility to ciprofloxacin (0% and 60%, respectively), although the former remained universally susceptible to ceftriaxone (100%) and trimethoprim-sulfamethoxazole (100%).

Conclusions: This analysis provides region-specific surveillance data describing the distribution and antimicrobial susceptibility of community bloodstream pathogens in British Columbia. The identification of *Salmonella* predominance in the Lower Mainland and reduced ciprofloxacin susceptibility among *E. coli* highlights the importance of ongoing provincial surveillance. These findings contribute to a better understanding of regional epidemiology and inform infection control and antimicrobial resistance monitoring initiatives in community health settings.

#21

NIKI SADAT AFJEH

Medical Student · Supervisor: **Dr. David F. Schaeffer**

NOBLE 81

TITLE

THE VANCOUVER GENERAL HOSPITAL GASTROINTESTINAL BIOBANK: SUPPORTING PANCREATIC CANCER RESEARCH

AUTHORS

Niki Sadat Afjeh[1], Maya Kevorkova[2], Shanzhao Wang[2], Martin Avancena[2], Rachel Windardi[2], Bruno Larcoa[2], Steve Kalloger[2], David F. Schaeffer[2]

AFFILIATIONS

[1]Department of Medicine, University of British Columbia, Vancouver, Canada; [2]Department of Pathology and Laboratory Medicine, University of British Columbia, Vancouver, Canada

ABSTRACT

Background/objectives: Pancreatic ductal adenocarcinoma (PDAC) remains a disease where, despite advances elsewhere, outcomes have changed little. For those of us caring for these patients, access to well-annotated tissue is essential to move the field forward. The VGH GI Biobank was established to support this work through a prospectively consented, institutionally governed collection.

Methods: We reviewed the biobank database to understand the availability and composition of pancreatic cancer specimens. Patient samples were characterized by histology and by the presence of plasma, frozen tissue, and FFPE material. Where needed, chart review was performed to improve clinical and specimen annotation.

Results: Pancreatic patient samples represent approximately 20% of the collection, with PDAC comprising the majority. Across 458 patient samples, biospecimen availability was variable but included a meaningful subset with matched plasma and tissue (frozen and FFPE), supporting both molecular and histopathologic studies.

As with many clinical biobanks, gaps in annotation were identified. Focused curation improved data completeness and, importantly, the ability to define clinically relevant cohorts.

Conclusions: From a clinical and research perspective, the value of the biobank lies not just in the number of samples, but in the ability to link high-quality specimens to meaningful clinical data. The VGH GI Biobank provides a structured, carefully stewarded resource to support pancreatic cancer research, with ongoing efforts focused on improving data quality and cohort definition to enable rigorous, hypothesis-driven studies.

#22

JOSEPH SILBURT

Medical Student

NOBLE 82

TITLE

DOES TUMOR ARCHITECTURE PREDICT MOLECULAR STATUS? EXPLORING THE APPLICATION OF NEURAL NETWORKS FOR HISTOLOGICAL FEATURE GENERATION

AUTHORS

Silburt, Joseph[1], Rasmussen, Sean[2]

AFFILIATIONS

[1] Department of Neuropathology, University of British Columbia, Vancouver, British Columbia, Canada; [2] Department of Pathology, Dalhousie University, Halifax, Nova Scotia, Canada

ABSTRACT

Background/objectives:

In recent years molecular markers have supplanted traditional metrics of tumor architecture , such as grade, when predicting cancer outcomes. However, with the rise of artificial intelligence, neural networks offer new opportunities for analyze complex patterns in data. In this exploratory analysis, we asked whether neural networks can identify morphological signatures of molecular status, and therein, add additional value in characterizing tumors.

Methods:

We analyzed 21 cases of esophageal adenocarcinoma collected in Atlantic Canada between 2024 and 2025. All samples were stained with H & E, MMR, PDL1, and HER2. H & E sections were converted to embeddings using UNI2, a general purpose pathology machine vision neural network. Embeddings were dimensionality reduced using uniform manifold approximation and projection (UMAP), and segmented into fuzzy clusters using a gaussian mixture model (GMM). Immunohistochemical stains were thresholded and normalized integrated density, and percentage area were assessed. Clustering analysis was performed using k-means clustering (k=2) and assessed via silhouette score. Statistical analysis was performed using ordinary least squares regression with an alpha of 0.05.

Results:

First we asked whether neural network generated features of H & E sections could predict molecular status. To generate features, we down sampled UNI2 generated embeddings using UMAP, and subsequently modeled the resulting distribution with a GMM, identifying three components to be optimal. Interestingly, we found that component 2 was associated with HER2 expression (relative risk: 0.30, p=0.027), this persisted after controlling for tumor size (relative risk 0.37, p=0.048). Similarly, after controlling for tumor size, component 1 was revealed to be associated with PDL1 expression (relative risk: 0.02, p=0.025). Next, we asked whether incorporating these morphological features help to define subpopulations of adenocarcinoma. Compared to a molecular only profile (silhouette score 0.287) incorporating components 2 (silhouette score: 0.294) and components 2 and 3 (silhouette score: 0.300) progressively improved clustering.

Conclusions:

This exploratory analysis demonstrates that tissue architecture, as captured via a general-purpose pathology neural network, predicts underlying molecular status, and informs the clustering of esophageal adenocarcinoma into subpopulations. Further work is needed to identify the underlying morphological signatures and connect these signatures with prognosis.

#23

PEIYAO WANG

Medical Student · Supervisor: **William Lockwood**

TITLE

HIGHLY PM2.5 EXPOSED PATIENTS WITH LUNG ADENOCARCINOMA HARBOUR A DISTINCT MUTATIONAL SIGNATURE DERIVED FROM PM2.5 EXPOSURE IN LUNG EPITHELIAL CELLS

AUTHORS

Wang, Peiyao[1], Julia, Naso[2], Myers, Renelle[2], Durney, Clinton[2], Granville, Joshua[1], Chuang, Yu-Chi[1], White, Justin[1], Bartolomeu, Crista[1], McGuire, Anna[2], MacAulay, Calum[1], Lam, Stephen[1], Lam, Wan[1], Lockwood, William[1]

AFFILIATIONS

[1]British Columbia Cancer Research Institute, Vancouver, BC; [2]Vancouver General Hospital, Vancouver, BC

ABSTRACT

Background/objectives: Lung cancer occurs in up to 25% of people who have never smoked. Exposure to outdoor air pollution, specifically PM2.5, defined as particulate matter less than 2.5 µm, has been associated with lung cancer risk in this population, but its role in lung cancer initiation remains undefined. This study explores the ability for PM2.5 to induce malignant transformation in vitro and its impact on the genome.

Methods:

BEAS-2B, a normal epithelial cell line, was exposed to PM2.5 via a 24-hour pulse-recovery schedule followed by a prolonged recovery period for a total of up to 12 weeks. Throughout the exposure timeline, cells were evaluated for various markers of malignant transformation, including increase in DNA damage and anchorage independent growth. These cells underwent single clone selection before being sent for whole genome sequencing to assess presence of mutational signatures. In addition, 116 lung patients with lung adenocarcinoma who had never smoked and had defined levels of PM2.5 exposure were sent for whole exome sequencing (WES).

Results: Long-term exposures of PM2.5 led to irreversible changes in cell morphology and significantly increased mutational burden. A significant dose-dependent increase in colony formation ability was also observed by soft agar assays, indicating increased anchorage independent growth. Analysis of the genome of these long-term exposure cells may reveal unique mutational signatures or pathways that are modified due to PM2.5 exposure. WES analysis of adenocarcinoma patients showed patients with higher PM2.5 exposure history trending towards being younger and possessing distinct mutational signatures such as SBS40a observed in the long-term exposure cells and lacking APOBEC mutational signatures compared to those with lower PM2.5 exposure.

Conclusions: PM2.5 has a role in lung cancer initiation in normal lung epithelial cells *in vitro*. Our findings also support a difference between lung adenocarcinoma patients with high and low PM2.5 exposure histories seen by different mutational profiles. Overall, this has the potential to inform screening and early detection of lung cancer, particularly in patients who have never smoked.

#24

MICHAEL ZHAO

Medical Student · Supervisor: **Dr. Diana N. Ionescu**

NOBLE 83

TITLE

BRIDGING THE DIFFERENCE: MEDICAL STUDENT EXPERIENCES WITH HISTOPATHOLOGY IN AN INTEGRATED CURRICULUM

AUTHORS

Zhao, Michael[1], Povshedna, Tetiana[2], Altow, Lynne[1], Hopkins, Jade[1], Ionescu, Diana N.[2,3]

AFFILIATIONS

[1]Faculty of Medicine, The University of British Columbia; [2]Department of Pathology and Laboratory Medicine, The University of British Columbia; [3]BC Cancer

ABSTRACT

Background/objectives: Histopathology (HP) teaching is a core component of undergraduate medical education. This study examines medical student perspectives on HP laboratories and clinical pathological correlation sessions (CPCs) within the University of British Columbia (UBC) Medical Undergraduate Program delivered in the first two years to shape curriculum improvement.

Methods: A cross-sectional Qualtrics survey was distributed to UBC medical students (n=103) via the Learner Advisory Access Council. Students rated HP labs and CPC sessions on a 0–10 Likert scale. Participants were stratified by training level: Year 1 (Y1, n=37), Year 2 (Y2, n=42), and Clinical years 3/4 (Y3/4, n=22). Descriptive statistics were used for analysis.

Results: Enjoyment of HP labs was mixed, with median scores ≤5 in Y1 and Y2, but higher when recalled in clinical years (median 7). Reported attendance was moderate in Y1 and clinical years (median >5), but lower in Y2 (median 3), which corresponded to higher independent review of lab content (median 8). Y2 students reported the highest perceived relevance of labs to clinical practice (median 6) and usefulness for learning weekly content (median 6), whereas Y1 students reported ratings ≤5 for both measures. Proposed improvements, including stronger integration with weekly clinical content and gamification, were supported by >50% of respondents. CPC sessions were well rated (≥5) for enjoyment, engagement, and perceived clinical relevance.

Conclusions: Student perceptions of HP teaching vary by training level, with lower perceptions of relevancy in preclinical years. Targeted curricular enhancements, including improved clinical integration, may enhance relevance, engagement, and educational effectiveness.

#25

MEHAK JUDGE

Undergrad · Supervisor: **Dr. Cheryl Wellington**

TITLE

CHOLESTERYL ESTER TRANSFER PROTEIN (CETP) EXPRESSION IN 5XFAD MICE: MINIMAL EFFECTS ON PERIPHERAL LIPIDS AND AMYLOID-β PATHOLOGY

AUTHORS

Judge, Mehak[1,2]; Poliakova, Tetiana[1,2]; Anwer, Mehwish[1,2]; Barron, Carlos[1,2]; Cheng, Tom[1,2]; Fan, Jianjia[1,2]; Wilkinson, Anna[1,2]; Wellington, Cheryl[1,2,3,4]

AFFILIATIONS

[1] Djavad Mowafaghian Centre for Brain Health, University of British Columbia, Vancouver, British Columbia, Canada; [2] Department of Pathology and Laboratory Medicine, University of British Columbia, Vancouver, British Columbia, Canada; [3] International Collaboration on Repair Discoveries, Vancouver, British Columbia, Canada; [4] School of Biomedical Engineering, University of British Columbia, Vancouver, British Columbia, Canada

ABSTRACT

The scientific questions underlying this study focus on the role of cholesteryl ester transfer protein (CETP), a key modulator of proatherogenic low-density lipoprotein (LDL) to antiatherogenic high-density lipoprotein (HDL) cholesterol ratio, in vascular contributions to cognitive impairment and dementia (VCID). Interest in CETP as a therapeutic target for VCID is increasing, as the CETP inhibitor obicetrapib was recently shown to stabilize Alzheimer's disease (AD) plasma biomarkers, particularly in APOE4 carriers. As obicetrapib is a safe and effective small molecule developed to reduce coronary artery disease, leveraging CETP inhibition to also mitigate VCID represents a high-priority objective in the field.

However, modeling CETP biology in rodents is challenging, as mice lack functional CETP, resulting in a naturally high HDL:LDL ratio and limiting the study of LDL-driven vascular mechanisms relevant to VCID. To address this, we employed a translational reverse-engineering approach to humanize peripheral lipoprotein metabolism in a 5xFAD mouse model of brain amyloidosis by introducing a human CETP transgene. We evaluated the effects of CETP expression and diet on lipid profiles and AD-relevant biomarkers.

Diet emerged as the dominant driver of lipid phenotypes, with the low-fat high-cholesterol diet supplemented with cholic acid markedly increasing both LDL and the LDL:HDL ratio across sexes. CETP effects were context-dependent rather than global, with minimal impact under most conditions. In cortex homogenates, soluble and insoluble amyloid-β measures were more variable and showed weaker, less consistent responses to diet and genotype.

Future studies will evaluate alternative CETP models and strategies to more robustly recapitulate human lipoprotein physiology, enabling more precise interrogation of CETP as a therapeutic target in VCID.

#26

JIHYUN LEE

BMLSc · Supervisor: **Tony Ng**

NOBLE 61

TITLE

RETROSPECTIVE STUDY OF HISTOPATHOLOGIC AND MOLECULAR RISK FACTORS FOR BRITISH COLUMBIA POPULATION COHORT OF ORAL DYSPLASIA

AUTHORS

Lee, Jihyun [1], Liu, Kelly Y.P. [1,2], Saleh, Daniyah [3], Poh, Catherine F. [1,2,3], Ko, Yen Chen Kevin [1,2,3], Ng, Tony L. [1,3]

AFFILIATIONS

[1] Affiliations; [2] Department of Pathology and Laboratory Medicine, The University of British Columbia, Vancouver, British Columbia.; [3] Department of Oral Biological and Medical Sciences, Faculty of Dentistry, University of British Columbia, 2199 Wesbrook Mall, Vancouver, BC V6T 1Z3, Canada.; [4] Department of Pathology and Laboratory Medicine, Vancouver General Hospital, Vancouver, British Columbia.

ABSTRACT

Background: Oral epithelial dysplasia (OED) refers to precancerous changes in the oral mucosa that carry a variable risk of progression to oral squamous cell carcinoma (OSCC)—a malignancy with high mortality and poor prognosis. The current histology-based grading system is limited by interobserver variability and suboptimal prognostic performance, particularly for low- and moderate-grade lesions. We have recently shown that p53 and p16 immunohistochemistry (IHC), reflecting alterations in *TP53* and *CDKN2A*, may improve risk stratification of OED, but correlation with outcome data using a large cohort remain lacking.

Methods: We conducted a retrospective study of a year-long population-based cohort of oral biopsy cases in a subspecialty oral pathology service. Cases included histologically diagnosed OED and selected non-dysplastic lesions at risk for progression. Clinical, demographic, and outcome data (recurrence, persistence, and progression to high-grade dysplasia or carcinoma) were collected (median follow-up 8.3 years). Histopathologic review and p53/p16 IHC were performed on selected cases. Kaplan–Meier survival analysis and Cox proportional hazards models were used to assess association with progression risk.

Results: A total of 231 lesion sites (235 patients) with ≥5 years of follow-up were analyzed (median follow-up 8.3 years). Overall, 36 lesions (15.6%) progressed to high-grade lesions, verrucous carcinoma, or OSCC. Kaplan–Meier analysis demonstrated significant separation in progression-free survival by biomarker status. p16 abnormality (n=87) was associated with early and sustained risk (log-rank $p<0.0001$), with curve divergence within 1–2 years. p53 abnormality (n=39) showed a more gradual but persistent increase in long-term risk. A stepwise risk gradient was observed: lesions with normal p53/p16 expression had the best prognosis, single-marker abnormalities conferred intermediate risk, and dual p53/p16 abnormalities showed the poorest outcomes. At 8 years, both p16 (HR 16.61, 95% CI 4.84–57.03; $p=8.02\times10^{-6}$) and p53 (HR 25.61, 95% CI 4.28–153.33; $p=3.83\times10^{-4}$) abnormalities were independently associated with progression, with similarly elevated risk in double-abnormal cases (HR 18.71, 95% CI 5.22–67.11; $p=6.95\times10^{-6}$).

Conclusions: p53 and p16 IHC provide strong prognostic value in OED, with p16 dysregulation associated with early progression, whereas p53 abnormality showed sustained long-term risk. Combined biomarker assessment identifies a high-risk subgroup with markedly worse outcomes. Integration of such biomarkers with histologic evaluation enhances risk stratification that can be utilized to optimize clinical management of OED.

#27

JUSTIN WONG

BMLSc · Supervisor: **Ali Bashashati**

NOBLE 62

TITLE

PROGNOSTIC MODELLING AND SPATIAL TRANSCRIPTOMIC ANALYSIS OF A 79-GENE IMMUNE PANEL IN GLIOBLASTOMA REVEALS C-TYPE LECTIN DOMAIN FAMILY 10 MEMBER A SPATIAL PATTERNS

AUTHORS

Wong, Justin Amen[1], Ali Bashashati[1, 2], Katherine Rich[3]

AFFILIATIONS

[1]Department of Pathology & Laboratory Medicine, University of British Columbia, Vancouver, BC V6T 1Z4, Canada; [2]School of Biomedical Engineering, University of British Columbia, Vancouver, BC V6T 1Z4, Canada; [3]Bioinformatics Graduate Program, University of British Columbia, Vancouver, BC V6T 1Z4, Canada

ABSTRACT

Background/objectives:

Glioblastoma (GBM) is a highly aggressive Grade IV brain tumor with poor prognosis and rapid progression. Tumor heterogeneity includes diverse cell populations and cellular states that contribute to tumor growth, immune evasion, and resistance to therapy. With a median survival of 15 months, effective risk stratification is critical for identifying high-risk patients and guiding clinical decisions. This study aimed to develop a prognostic gene risk model for GBM and examine the spatial expression pattern of a selected candidate gene, C-type lectin domain family 10 member A (CLEC10A), an immune-related gene associated with Type-2 conventional dendritic cells (cDC2s).

Methods:

Gene expression and clinical data for GBM patients were obtained from The Cancer Genome Atlas (TCGA). Data preprocessing included removing duplicates and missing values, and clinical data were matched to the expression dataset using TCGA patient barcodes. The matched dataset was split into training (75%) and validation (25%) cohorts. Univariate Cox identified genes with $p < 0.05$ for inclusion in a LASSO Cox model tuned using five-fold cross-validation to construct a prognostic gene panel. Risk scores were calculated and a maxstat cutpoint was used to classify patients into high-risk and low-risk groups. Survival differences between groups were evaluated using Kaplan–Meier analysis.

Spatial transcriptomic data from a publicly available adult brain GBM section were obtained from the 10x Genomics dataset repository and were analyzed using Xenium Explorer v4.1.1.

Results:

The LASSO model successfully stratified the risk groups in the validation set with a validation C-index of 0.656, notable given the substantial heterogeneity of GBM and the influence of external factors such as age on survival. Kaplan-Meier analysis showed a significant survival difference between risk groups ($p = 0.018$).

The spatial distribution of CLEC10A in the GBM section was generally low and diffuse (nCount = 2,111) with no region of pronounced expression. Additional immune markers were examined including ITGAX (cDC1), CD4 (T helper cells) and CD8b (cytotoxic T cells). ITGAX (n = 115,488) and CD4 (n = 129,206) were highly concentrated within a localized tissue region indicating immune infiltration, whereas CD8b expression (n = 8,349) remained relatively low and diffusely distributed.

Conclusions:

Previous studies show that cDC1s can activate and recruit CD8+ T cells through chemokine (C-X-C motif) ligand 9 (CXCL9). However, cDC1s may be suppressed in GBM by factors within the tumor microenvironment, potentially limiting CD8+ T-cell recruitment. It has been shown that cDC2s can partially compensate for the defective cDC1s by supporting CD8+ T-cell activation. A proposed mechanism is that cDC2s compensate by activating CD8+ T cells, but are unable to produce adequate levels of CXCL9s to attract T cells to the site of migration**.** This pattern is consistent with the diffuse spatial distributions observed in CD8b and CLEC10a, which do not show clear accumulation within the localized immune region.

#28

MATTHEW YAP

BMLSc · Supervisor: **Dr. Gang Wang**

NOBLE 63

TITLE

MARKER-SPECIFIC VALIDATION OF AN AUTOMATED IMMUNOHISTOCHEMISTRY H-SCORE QUANTIFICATION PIPELINE IN MUSCLE-INVASIVE BLADDER CANCER

AUTHORS

Matthew Yap[1], Ioana-Maria Mihai[1,2], Maram Alanazi[2], Gheorghe-Emilian Olteanu[3], Alberto Contreras-Sanz[4], Peter Black[4], Gang Wang[1,2*]

AFFILIATIONS

[1] Department of Pathology and Laboratory Medicine, BC Cancer, Vancouver, BC, Canada; [2] Department of Pathology and Laboratory Medicine, University of British Columbia, Vancouver, BC, Canada; [3] Cellular Pathology Department, Royal Brompton Hospital, London, United Kingdom; [4] Department of Urologic Sciences, University of British Columbia, Vancouver, BC, Canada

ABSTRACT

Background/objectives:

Immunohistochemistry (IHC) plays a central role in subtyping of muscle-invasive bladder cancer (MIBC), yet conventional semi-quantitative scoring lacks objectivity and scalability. Automated digital pathology offers potential solutions, but requires robust, marker-specific validation against expert consensus scoring. This study aimed to evaluate the analytical validity and feasibility of automated IHC H-score quantification in MIBC.

Methods:

We developed and internally validated an automated digital pathology pipeline for continuous IHC H-score quantification using QuPath (v0.6.0-arm64). Tissue microarrays (TMAs), each containing 84 tissue-containing cores, were generated from transurethral resection of bladder tumor (TURBT) specimens from a retrospective cohort of 42 patients with neoadjuvant chemotherapy (NAC)-treated MIBC at Vancouver General Hospital. Cell detection was performed using StarDist (v0.9), followed by automated intensity-based H-score calculation for two basal markers (CK14, CK5/6) and two luminal markers (CK20, Uroplakin II). H-scoring was then restricted to tumor epithelium by object-level classification using a supervised tumor/non-tumor classifier trained on pathologist-reviewed annotations. Automated scores were compared with consensus scores from three blinded pathologists using Pearson correlation, linear regression, intraclass correlation coefficients (ICC), and Bland–Altman analysis.

Results:

Automated H-scores demonstrated strong agreement with pathologist consensus across all four markers. CK14 showed near-perfect agreement (ICC ≈ 0.99) with minimal bias and narrow limits of agreement. CK20 also demonstrated high agreement (ICC ≈ 0.95). CK5/6 and Uroplakin II demonstrated slightly lower agreement (ICC ≈ 0.92–0.93) with mild proportional bias. Across markers, the automated pipeline preserved a broad H-score range, with range ratios of 0.96–0.99.

Conclusions:

This study establishes a robust, methods-forward pipeline for automated continuous IHC H-scoring in MIBC. The internally validated framework provides a scalable foundation for external cohort validation and future clinical outcome-associated biomarker analyses.

#29

ABTEEN ARAB

Undergrad · Supervisor: **Dr(s). Ali Bashashati & Maziar Riazy**

TITLE

WHEN DO GLOMERULAR SEGMENTATION MODELS FAIL? A BENCHMARK OF GLOMERULAR SEGMENTATION IN PEDIATRIC, DISEASED, AND VARIABLY STAINED KIDNEY TISSUE

AUTHORS

Arab, Abteen[1], Brown, Kelly[2,3], Morishita, Kimberly[2,3], Bashashati, Ali[1,4], Riazy, Maziar[4,5]

AFFILIATIONS

[1] School of Biomedical Engineering, University of British Columbia; [2] Department of Pediatrics, University of British Columbia Faculty of Medicine; [3] BC Children's Hospital Research Institute; [4] Pathology and Laboratory Medicine, University of British Columbia; [5] The Renal Pathology Laboratory for British Columbia, St. Paul's Hospital

ABSTRACT

Introduction: In renal pathology, identification of the glomeruli is a central component of biopsy assessment. Despite recent advances of AI-based glomerular segmentation, most models have primarily been evaluated on adult tissue, limited diseased glomeruli, and periodic acid Schiff (PAS)-stained sections. As a result, their generalizability to pediatric patients, diseased glomeruli, and alternative stain domains remains largely unexplored.

Objectives: In this study, we benchmark glomerular segmentation models across several clinically relevant sources of variation. Specifically, we compare performance in adult versus pediatric tissue, normal versus diseased glomeruli, and PAS versus non-PAS stain settings. Additionally, we assess whether computational stain transfer methods that convert non-PAS stains into a PAS-like stains improve segmentation performance.

Methods: We used two datasets in this analysis: the Pediatric Vasculitis Project (PedVAS) and the adult Kidney Precision Medicine Project (KPMP). The PedVAS cohort included 192 whole-slide images (WSI) from glomerulonephritis cases and 16 normal control WSI across four stains (H&E, PAS, silver, and trichrome). The KPMP cohort included 16 normal control WSI with the same stains. All annotations were reviewed by pathologists. Seven glomerular morphologies were assessed: normal, necrosis, sclerosis (nodular, segmental, & global), and crescents (cellular & fibrous).

Benchmarking was performed using pre-trained glomerular segmentation models from the KPI Challenge, evaluated using Dice score (0 = no overlap, 1 = perfect segmentation). We also evaluated the effect of transferring non-PAS stains into a PAS-like domain as a preprocessing step on segmentation performance using unsupervised generative models.

Results: Across models, we observed no significant difference in segmentation performance between adult and pediatric patients, suggesting that age alone is not a barrier to generalization. In contrast, segmentation performance decreased across all diseased glomerular morphologies, with an average drop of 0.37 Dice compared to normal glomeruli. Performance also varied across stains, with PAS yielding the strongest results (Dice = 0.92), followed by silver (Dice = 0.60), while H&E and trichrome showed substantially lower performance (Dice = 0.19 and 0.23, respectively). Computational stain augmentation improved performance on non-PAS stains by an average of 0.29 Dice.

Conclusion: This study shows that glomerular segmentation models perform well on simplified datasets dominated by healthy glomeruli and PAS-stained slides, but perform significantly worse on clinically relevant datasets containing diseased glomeruli and stains with weaker GBM contrast (H&E and trichrome). Computationally augmenting these stains into a common stain space significantly improved performance, suggesting that stain-transfer as a preprocessing step before model training may improve overall performance and model generalizability. Taken together, our results highlight the need for more robust glomerular segmentation models, evaluated on clinically applicable datasets, that better capture biological heterogeneity.

#30

DANIELLE KEITH

Undergrad · Supervisor: **Dr. Marc Horwitz**

TITLE

EPSTEIN-BARR VIRUS DRIVES A TH1 PHENOTYPE IN A MOUSE MODEL OF PSORIATIC ARTHRITIS

AUTHORS

Keith, Danielle[1] , Allanach, Jess[1,2], Horwitz, Marc[1,2]

AFFILIATIONS

[1]Department of Microbiology & Immunology, the University of British Columbia; [2]Experimental Modelling Facility, Life Sciences Institute

ABSTRACT

Background: Epstein Barr virus (EBV) is a ubiquitous herpesvirus implicated in the pathogenesis of multiple autoimmune diseases through its ability to establish lifelong latency and alter host immune responses. While EBV-associated immune dysregulation has been studied in several autoimmune conditions, its role in psoriatic arthritis (PsA) remains underexplored. PsA is a heterogeneous inflammatory disease involving complex interactions between innate and adaptive immune cells in skin and joint tissues. This study aims to determine whether latent EBV-like infection promotes a T helper 1 (Th1) driven immune response in a mouse model of PsA.

Methods: Transgenic T-bet-ZsGreen C57BL/6 mice are infected with murine gammaherpesvirus-68, a homolog of EBV, in the intraperitoneal cavity. Viral latency is established after 5 weeks whereafter PsA-like disease is simulated through weekly injections of mannan polysaccharide. Mice are scored daily over a 24 day period for assessment of erythema and desquamation severity. At endpoint, immune cell infiltration, activation, and polarization are assessed in the knee joint, skin, and secondary lymphoid tissues using flow cytometry.

Results: Preliminary results indicate that latent gammaherpesvirus-68 infection enhances immune activation in both peripheral and disease-relevant tissues. This is accompanied by increased frequencies of inflammatory lymphocyte populations and shifts in myeloid cell composition, consistent with a Th1-skewed immune phenotype.

Conclusions: These findings suggest that latent viral infection can amplify inflammatory immune responses and promote Th1 polarization in psoriatic arthritis. This work provides a framework for understanding how persistent viral infections contribute to autoimmune disease progression and may inform the development of targeted therapeutic strategies.

#31

AHMED MAKHLOUF

Undergrad · Supervisor: **Eugene Yeung**

NOBLE 64

TITLE

APPLICATION OF CUMULATIVE ANTIMICROBIAL SUSCEPTIBILITY DATA TO INFORM ORAL THERAPY IN JOINT INFECTIONS

AUTHORS

Makhlouf, Ahmed[1]; Yeung, Eugene[1,2,3]

AFFILIATIONS

[1]UBC Faculty of Pharmaceutical Sciences, [2]UBC Faculty of Medicine, [3]SFU School of Medicine

ABSTRACT

Background/objectives:

Joint infections can cause severe joint damage without early and effective treatment. Recently, clinical practices evolved from intravenous antimicrobials to oral therapies. Optimal treatment requires antimicrobial resistance patterns, which are often limited. This study aimed to produce an antimicrobial susceptibility report and provide guidance on oral antimicrobials in joint infections.

Methods:

A retrospective analysis encompassing 2020-2024 was performed using joint fluid specimen data from LifeLabs BC microbiology laboratories. Collected specimens were cultured to identify microorganisms and conduct antimicrobial susceptibility testing. *Staphylococcus* species were routinely tested with cloxacillin, clindamycin, cefazolin, and vancomycin.

Results:

275 processed specimens indicated growth, with the most common organisms being methicillin-resistant (MRSA), methicillin-susceptible (MSSA), and other Staphylococcus aureus (SOSA). High susceptibility rates were observed for tetracycline and sulfamethoxazole-trimethoprim.

Conclusions:

Tetracycline and sulfamethoxazole-trimethoprim may be effective oral antimicrobial agents for joint infections. However, clindamycin and erythromycin may not be beneficial oral antimicrobial options in comparison to intravenous therapies.

#32

DILNAR MAMATYUSUF

Undergrad · Supervisor: **Dr. Eugene Yeung**

TITLE

ENHANCED ANTIBIOGRAM OF CARBAPENEM-RESISTANT UROPATHOGENS IN BRITISH COLUMBIA: A RETROSPECTIVE ANALYSIS

AUTHORS

Dilnar Mamatyusuf [1], Eugene Y. H. Yeung[1,2,3]

AFFILIATIONS

[1]Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, BC, Canada; [2]Faculty of Medicine, University of British Columbia, Vancouver, BC, Canada; [3]School of Medicine, Simon Fraser University, Surrey, BC, Canada

ABSTRACT

Background/objectives:

Carbapenem-resistant pathogens pose a growing public health concern, as there are limited therapeutic options for treating the infections. Common uropathogens, including *Escherichia coli*, may exhibit resistance through carbapenemase production. Antimicrobial resistance patterns vary regionally, yet current treatment guidelines are largely based on non-local data and may not reflect the resistance trends in British Columbia (BC). In addition, recommended therapies often include non-formulary medications that are administered intravenously, delaying patient access in community. Our objective is to determine antimicrobial susceptibility patterns of Carbapenem-resistant uropathogens (CRU) in BC, to support empirical treatment decision-making for community practitioners.

Methods:

We analyzed urine culture and antimicrobial susceptibility testing data obtained from LifeLabs BC's microbiology regional laboratories in Surrey, Victoria, and Kamloops between January 1, 2023 and December 31, 2024. Only first isolates from patients of all ages and genders were included. Meropenem non-susceptibility was used to screen for carbapenem-resistant organisms, and carbapenemase genes were detected by polymerase chain reaction. Enhanced antibiogram was constructed for organisms with sample size > 30. Differences in antibiotic susceptibility were assessed using two-tailed chi-square or Fisher's exact tests ($p<0.05$).

Results:

Among 90,902 urine samples, 189 were meropenem non-susceptible. *E. coli* was the most common meropenem non-susceptible *Enterobacterales*, with 35 of 40 isolates carrying New Delhi metallo-beta-lactamase (NDM) and/or oxacillinase (OXA-48) genes. Fosfomycin showed highest activity against meropenem non-susceptible *E. coli* (>90% susceptibility), significantly exceeding that of nitrofurantoin for all isolates (95% vs. 53%), and in NDM-positive isolates (93% vs. 60%). *Pseudomonas aeruginosa* was the most common meropenem non-susceptible organism overall, with 60-82% susceptibility to routine antimicrobials, including ciprofloxacin.

Conclusions:

Carbapenem-resistant uropathogens demonstrate susceptibility patterns that differ from commonly cited data. Oral treatment options remain viable for common CRU, and the empiric use of non-formulary intravenous antimicrobials recommended by current guidelines may be unnecessary. These findings highlight the importance of incorporating local antibiograms to guide empiric therapy and improve access to effective outpatient treatment.

#33

ALINA YU

Undergrad · Supervisor: **Cheryl Wellington**

NOBLE 65

TITLE

HOW DIET INFLUENCES ALZHEIMER'S DISEASE PATHOLOGY: AMYLOID-BETA PLAQUE QUANTIFICATION IN TRANSGENIC MICE MODELS

AUTHORS

Alina Yu[1,2], Tetiana Poliakova[1,2], Anna Wilkonson[1,2], Mehwish Anwer[1,2], Carlos Barron[1,2], Tom Cheng[1,2], Jianjia Fan[1,2], Cheryl Wellington[1,2]

AFFILIATIONS

[1]Department of Pathology and Laboratory Medicine, University of British Columbia; [2]Djavad Mowafaghian Centre for Brain Health, University of British Columbia, Vancouver, Canada

ABSTRACT

Currently, more than 55 million people worldwide lives with dementia, with Alzheimer's Disease (AD) being the predominant type. AD has a complex pathology involving the accumulation of amyloid beta plaques and neurofibrillary tau tangles in the brain, resulting in progressive cognitive decline. Modifiable risk factors for AD include cardiovascular factors. Specifically, cholesteryl ester transfer protein (CETP), a key regulator of lipoprotein exchange, has emerged as a potential dementia therapeutic target. However, the exact mechanisms of how CETP affects AD pathology has yet to be studied, largely because mice, a frequently used AD model, lack CETP naturally. We hypothesize that transgenic CETP reconstitution in mice will exacerbate brain amyloidosis in the 5xFAD mice, which express human APP and PSEN1 transgenes with a total of five AD-linked mutations. To study this, we conduct histology analysis on 6-month-old 5xFAD female and male mice with or without CETP human mini gene. Immunohistostaining is performed on brain slices using 6E10 antibody, which binds to abnormally processed isoforms as well as precursor forms of amyloid beta. Then, the slides are scanned and analyzed through ImageJ and Fiji to quantify amyloid beta load per slide in area percentage. We expect to see higher levels of amyloid deposits in CETPx5xFAD mice compared to 5xFAD mice, and higher amyloid beta levels in female compared to male mice. These results will elucidate the relationship between CETP, diet and dementia progression, potentially paving the way for CETP inhibitors to become an effective AD treatment.

#34

GAEA LOUISE BUENAVENTURA

MSc student · Supervisor: **Ying Wang**

TITLE

DEVELOPING A 3D CO-CULTURE MODEL TO STUDY CELLULAR RESPONSES FOLLOWING PERCUTANEOUS CORONARY INTERVENTION

AUTHORS

Buenaventura, Gaea[1,2], Chatha, Aakar[1,2], Sun, Tao[2], Kong, Hyejin Julia[2], Elishaev, Maria[1,2], Samra, Amrit[2], Sahin, Basak[2], Walley, Keith[2,4], Lai, Chi[3], Yao, Yuan[2,5,6], and Wang, Ying[1,2]

AFFILIATIONS

[1]Department of Pathology and Laboratory Medicine, University of British Columbia, Vancouver, British Columbia, Canada; [2]Centre for Heart Lung Innovation, University of British Columbia, Vancouver, British Columbia, Canada; [3]Division of Anatomical Pathology, Providence Health Care, St. Paul's Hospital, Vancouver, British Columbia, Canada; [4]Division of Critical Care, Providence Health Care, St. Paul's Hospital, Vancouver, British Columbia, Canada; [5]Department of Mechanical Engineering, University of British Columbia, Vancouver, British Columbia, Canada; [6]Division of Cardiology, Department of Medicine, University of British Columbia, Vancouver, British Columbia, Canada

ABSTRACT

Background/objectives: Drug-eluting stents reduce in-stent restenosis by releasing anti-proliferative drugs that suppress smooth muscle cell (SMC) growth after percutaneous coronary intervention (PCI). However, the non-specific effects of these drugs delay re-endothelialization and promote chronic inflammation, causing restenosis in 5-10% of patients. Current models of PCI employ simplistic monocultures that overlook cell crosstalk or the extracellular matrix (ECM) in the injured blood vessels, whereas expensive animal models are not suitable for high-throughput drug screening. Therefore, physiologically relevant and cost-effective preclinical tools are needed. Collagen type 1 is the major ECM component in diseased blood vessels that require PCI. Furthermore, spatial transcriptomics data from our lab show that SMCs in the collagen-rich fibrous cap of atherosclerotic lesions display a synthetic phenotype rather than a contractile phenotype in a culture dish, suggesting that monocultured SMCs may not respond to injury or treatment as they do in injured vessels. We hypothesize that A 3D collagen hydrogel co-culture model can simulate cellular responses after vascular injury and support drug screening.

Methods: Human coronary artery SMCs were embedded in a rat tail collagen type 1 (2.5mg/mL) hydrogel or seeded on a plate then cultured for 3 days, followed by RT-qPCR to assess phenotype. To form the co-culture system, human coronary artery ECs were seeded atop the SMC-containing hydrogel to form a monolayer. After two days, a 1mm deep scratch to mimic PCI injury was made across the gel. EC activation was assessed 24 hours post-injury by intercellular adhesion molecule-1 (ICAM-1) immunofluorescence. SMC proliferation was evaluated 48 hours post-injury with an EdU flow cytometry assay. To assess inflammation after injury, apoptotic THP-1 macrophages were embedded under the SMC layer in the co-culture system to mimic injured vessels with a necrotic core. Fluorescently labelled THP-1 monocytes were added in the cell culture media and their infiltration into the hydrogel was determined 24 hours after the scratch.

Results: Collagen-embedded SMCs displayed reduced myosin heavy chain 11 expression and increased platelet-derived growth factor receptor-β expression, indicating that the 3D culture system can allow a synthetic SMC phenotype that mimic the cell status in vivo. Scratch injury increased ICAM-1 expression in EC and SMC proliferation near scratched areas. Monocytes infiltrate into scratched hydrogels and the infiltration further increased with more apoptotic cells embedded in the gel.

Conclusions: Our observations recapitulate early responses to injury post-PCI. Incorporating ECM results in a more physiologically relevant SMC phenotype. The co-culture system shows promise as a cost-effective preclinical drug-screening tool that can model diseased vessels and simulate human responses following injury.

#35

TIFFANY CHEN

MSc student · Supervisor: **Angela Devlin**

NOBLE 67

TITLE

UNDERSTANDING THE EFFECT OF FOLIC ACID ON BETA-CELL FUNCTION

AUTHORS

Tiffany Chen[1], Zoe Lofft[1], Francis Lynn[2], Angela M Devlin[3]

AFFILIATIONS

Departments of Pathology and Laboratory Medicine[1], Surgery[2], and Pediatrics[3], The University of British Columbia; BC Children's Hospital Research Institute.

ABSTRACT

Background/objectives:

Folic acid, a synthetic oxidized form of a B-vitamin, is recommended before and during pregnancy to reduce the risk of neural tube defects. However, several Canadian birth cohorts estimate that pregnant women are consuming 2-5 times more than the recommended supplement level. Previous studies have reported that excess folic acid intake during pregnancy adversely affects the metabolic health of both mothers and their children, yet the mechanisms remain unclear. The pancreas is the second largest depot of folate in the body, but little is known about the role of folates in insulin-producing beta-cell function. Initial studies in mouse models show that over-supplementation with folic acid alters beta-cell mass in both mothers and offspring, suggesting that folic acid levels may directly influence beta-cell biology. We therefore hypothesize that high levels of folic acid negatively affect beta-cell function and identity by impairing the production of 5-methyltetrahydrofolate (5MTHF) and downstream S-Adenosylmethionine (SAM)-mediated histone methylation.

Methods:

Human embryonic stem cell–derived beta-cells (SCbeta-cells) will be used to determine the effects of folic acid and 5MTHF on glucose-stimulated insulin secretion. Histone H3K4me3 modifications, beta-cell identity markers, and changes in folate-related metabolites will also be determined. Rescue experiments with 5MTHF and CRISPR/Cas9-mediated MTR knockouts will be used to further clarify the pathway. These studies will provide mechanistic insight into how folic acid influences beta-cell function. This is an important islet study that also benefits diabetes research and informs guidelines for folic acid intake in pregnancy.

Results:

Preliminary glucose-stimulated insulin secretion data suggest that 200 nM folic acid (a supraphysiological level) impairs insulin secretion in stem cell–derived beta-cells, while 100 nM folic acid (approximately 5 fold higher than physiological levels) causes a modest reduction in insulin secretion.

We also examined histone methylation changes in postnatal day 14 mouse liver from offspring of dams fed a 10× folic acid diet. Multiplex histone profiling revealed significant up- and downregulation of histone modifications associated with beta-cell identity genes, including H3K18ac and H3K4me3.

Conclusions:

These findings suggest that supraphysiological folic acid exposure may impair beta-cell function and alter epigenetic regulation associated with beta-cell identity. Together, our data support a potential mechanistic link between excess folic acid intake and disrupted one-carbon metabolism, leading to altered histone modifications and impaired insulin secretion. Ongoing studies will further define the causal role of 5MTHF and SAM-mediated methylation in mediating these effects.

#36

GAHAN DIWAN

MSc student · Supervisor: **David Granville**

NOBLE 68

TITLE

GRANZYME B AS A DRIVER OF IMMUNOMODULATION AND ATROPHIC SCARRING IN DISCOID LUPUS ERYTHEMATOSUS

AUTHORS

Diwan, Gahan[1,3,4], Crawford, Richard[1,2], Granville, David[1,3,4]

AFFILIATIONS

[1] Department of Pathology and Laboratory Medicine, University of British Columbia, Vancouver, Canada; [2] Department of Dermatology and Skin Sciences, University of British Columbia, Vancouver, Canada; [3] International Collaboration on Repair Discoveries (ICORD) Centre, Vancouver Coastal Health Research Institute, University of British Columbia, Vancouver, Canada; [4] British Columbia Professional Firefighters' Burn and Wound Healing Group, Vancouver Coastal Health Research Institute, University of British Columbia, Vancouver, Canada

ABSTRACT

Background: Cutaneous lupus erythematosus (CLE) is a complex inflammatory skin condition with a prevalence of 73–109 per 100,000 people, showing a higher predominance in women. The chronic form of CLE, discoid lupus erythematosus (DLE), manifests as inflammatory plaques that result in atrophic scarring. DLE is characterized by an interferon-driven cytotoxic anti-epidermal response that progresses into a chronic stage of innate and adaptive immune reactivation, ultimately leading to dyspigmented inflammatory plaques and atrophic scarring. Growing evidence from spatial transcriptomics and histopathological studies shows elevated levels of extracellular granzyme B (GzmB) and immune cell infiltration in DLE lesions. However, it remains unclear how extracellular GzmB shapes immune responses and contributes to atrophic scarring in later stages of DLE pathophysiology. **I hypothesize that GzmB acts as an immunomodulatory protease in DLE by cleaving substrates to modulate their activity within the tissue microenvironment, thereby shaping immune polarization and promoting atrophic scarring**.

Methods: We first identified the major cellular sources of GzmB in DLE skin lesions and investigated its role in shaping immune responses. By performing transcriptomic analyses on immune cells in vitro, we assessed how GzmB influences immune cell behavior. To further identify substrates cleaved by GzmB, we employed an unbiased degradomic approach using terminal amine isotopic labeling of substrates (TAILS) coupled with mass spectrometry. Candidate substrates were subsequently validated using in vitro cleavage assays and correlated with disease pathology to determine their relevance in DLE progression.

Results: Preliminary findings suggest that GzmB-positive cells occur during the inflammatory phases of disease, with innate and adaptive immune cells being the major producers. We expect that GzmB-targeted substrates and the resulting fragments in DLE are involved in decorin cleavage, collagen degradation, and impaired remodeling, ultimately leading to atrophic scarring.

Conclusions: DLE is a debilitating inflammatory skin disease with limited therapeutic options. These studies will advance our understanding of GzmB as an immunomodulatory enzyme and uncover potential substrates and biomarkers of disease activity in DLE and related chronic inflammatory skin disorders.

#37

TISHA HAUKONGO

MSc student · Supervisor: **Dr. Hélène F. Côté**

TITLE

INVESTIGATING LINE-1 EXPRESSION IN WOMEN LIVING WITH AND WITHOUT HIV

AUTHORS

Haukongo, Tisha[1], Afe, Michael[1], Cai, Loulou[1], Gadawska,Izabelle [1], Kaida, Angela[2,3,5], King, Elizabeth M[2,3,4,5,8], Murray, Melanie CM [2,3,4,7,8], Cote, Helene CF[1,2,3,6,7] on behalf of the British Columbia CARMA-CHIWOS Collaboration (BCC3; CIHR CTN+ 335)

AFFILIATIONS

Department of Pathology and Laboratory Medicine, The University of British Columbia[1]; Women's Health Research Institute, British Columbia Women's Hospital and Health Centre[2]; CIHR Pan-Canadian Network for HIV and STBBI Clinical Trials Research (CTN+)[3]; Department of Medicine, University of British Columbia [4]; Faculty of Health Sciences, Simon Fraser University[5]; Centre for Blood Research, University of British Columbia[6]; Edwin S.H. Leong Healthy Aging Program, University of British Columbia, Vancouver[7]; Oak Tree Clinic, British Columbia Women's Hospital and Health Centre[8]

ABSTRACT

Background/objectives:

Long Interspersed Nuclear Element-1 (LINE-1) is the only autonomously active transposable element in the human genome, representing ~17% of genomic DNA. Although most LINE-1 copies are inactive, a small subset retains the capacity to complete the retrotransposition cycle, which involves transcription into RNA, translation of LINE-1-encoded proteins, reverse transcription, which may lead *to de novo* genomic integration. Epigenetic mechanisms normally suppress LINE-1 activity to maintain genomic stability; however, this regulation may weaken with age, allowing increased LINE-1 activity and the accumulation of LINE-1 RNA and reverse-transcribed DNA. These nucleic acid intermediates are linked to cellular stress, inflammation, and age-related diseases.

Human immunodeficiency virus (HIV) infection provides a clinically relevant context for studying LINE-1 activity, as persistent immune activation can occur despite effective antiretroviral therapy (ART). Additionally, nucleoside reverse transcriptase inhibitors widely used in ART regimens, inhibit the reverse transcription step of the viral life cycle, a process that also occurs during LINE-1 replication. This raises the possibility that long-term ART exposure may influence endogenous LINE-1 activity.

This study aims to quantify LINE-1 activity at both the DNA and transcriptional levels in women living with and without HIV, and to examine associations with age, ART exposure, and systemic inflammatory markers.

We hypothesize that LINE-1 activity at the DNA and transcriptional level differs according to HIV status and age, and is associated with systemic inflammatory markers. We further hypothesize that exposure to reverse transcriptase inhibitor–containing ART is associated with altered LINE-1 activity.

Methods:

Participants are selected from the British Columbia CARMA-CHIWOS Collaboration (BCC3) cohort of women living with and without HIV who share similar social determinants of health and exposures. Genomic DNA will be extracted from whole blood, and LINE-1 DNA content quantified using monochrome multiplex qPCR targeting LINE-1 ORF2 and the single-copy reference gene albumin. RNA will be extracted from whole blood, followed by cDNA synthesis and qPCR to assess LINE-1 transcriptional expression normalized to beta-actin. Associations between LINE-1 DNA copy number, LINE-1 mRNA level and relevant variables, including age, HIV status, and ART exposure, will be evaluated using multivariable regression models.

Results:

Preliminary feasibility work has confirmed successful extraction and quantification of nucleic acids from stored cohort samples. It is anticipated that LINE-1 molecular markers will vary according to HIV status and inflammatory burden.

Significance:

This study will improve understanding of the relationship between endogenous LINE-1 activity and long-term exposure to antiretroviral therapy in women living with HIV. Characterizing LINE-1 activity in this clinical context may inform future investigations into molecular mechanisms linking chronic immune activation, inflammation, and age-associated comorbidities in HIV.

#38

VIVIAN HO

MSc student · Supervisor: **Ying Wang**

TITLE

PREDICTING THE CARDIOVASCULAR OUTCOMES OF ANTI-CANCER AXL INHIBITORS

AUTHORS

Ho, Hsing-Wei[1,2], Elishaev, Maria[1,2], Buenaventura, Gaea L.[1,2], Mao, Yuancheng[1,2], Reece, Nina[1,2], Chatha, Aakar[1,2], Leung, Samuel[1,2], Sun, Tao[1,2], Kong, Hyejin Julia[1,2], Lai, Chi[1,2,3], and Wang, Ying[1,2].

AFFILIATIONS

[1]Department of Pathology and Laboratory Medicine, University of British Columbia. Vancouver, BC, Canada. [2]Centre for Heart Lung Innovation, University of British Columbia. Vancouver, BC, Canada. [3]Division of Anatomical Pathology, Providence Health Care, St. Paul's Hospital. Vancouver, BC, Canada.

ABSTRACT

BACKGROUND/OBJECTIVES: Cancer and coronary artery disease (CAD) are two leading causes of mortality globally. Most cancer patients aged 40 years and older have CAD and these atherosclerotic lesions are directly exposed to anti-cancer drugs. Evidence has correlated the cardiotoxicity of anti-cancer treatments with higher risk of CAD-related death in cancer patients. Most cases of CAD-related deaths are due to plaque rupture. Studies have shown that efferocytosis, the process by which macrophages clear apoptotic cells within lesions, is critical for preventing the progression of stable plaques to rupture-prone plaques. AXL, a macrophage surface receptor, and its ligand GAS6, are key mediators for efferocytosis in both human and mouse. The AXL-GAS6 signaling axis is also involved in tumor progression. Several AXL inhibitors are therefore now in clinical trial to treat cancer by disrupting AXL-GAS6 interaction. However, their potential impact on macrophage function, and thus cardiovascular health, is still unknown. Therefore, it is important to assess the effect of AXL inhibitors on CAD progression to proactively mitigate any side effects. We hypothesize that AXL inhibitors will accelerate plaque destabilization by inhibiting efferocytosis. This pilot study aims to determine the effect of anti-cancer AXL inhibitor on the stability of atherosclerotic lesions in vivo.

METHODS: To induce atherosclerotic plaque formation, C57BL/6 mice were injected with PCSK9-encoding adenovirus (AAV-PCSK9) intravenously and maintained on high-fat diet (HFD). Control mice were injected with luciferase-encoding adenovirus (AAV-Luc). After 16 weeks of HFD, mice were treated with Dubermatinib, an AXL inhibitor used as a monotherapy for cancer. To simulate clinical trial treatment regimens, Dubermatinib was administered at 10.25 mg/kg by oral gavage for 3 weeks. Mice were sacrificed one hour after the final dose.

To assess lesion stability, future work will utilize histological staining to determine lesion size, necrotic core size, and fibrous cap thickness. Multiplex imaging will be used to determine the expression levels of AXL signaling markers, efferocytosis molecules, and inflammatory cytokines to implicate whether changes in lesion morphology is due to impaired efferocytosis.

RESULTS: AAV-PCSK9 mice total cholesterol levels were 5 times higher than AAV-Luc mice on HFD, and 9 times higher than C57BL/6 mice on normal chow, confirming successful induction of hypercholesterolemia.

Histological analysis is expected to reveal larger atherosclerotic lesions with expanded necrotic cores and thinner fibrous caps, which are indicative of plaque destabilization. Complementary multiplex imaging is expected to show reduced AXL signaling, accumulation of apoptotic cells, and elevated pro-inflammatory markers, which would demonstrate impaired efferocytosis and provide mechanistic context for the changes in lesion morphology.

CONCLUSION: Preliminary results confirmed the feasibility of using AAV-PCSK9 mouse in modeling hypercholesterolemia-induced atherosclerosis. Histological analyses are ongoing to reveal the potential effects of AXL inhibitors on atherosclerotic lesions.

#39

ZOE HORLICK

MSc student · Supervisor: **Dr. Brian Kwon**

TITLE

VALIDATION OF SERUM GLIAL FIBRILLARY ACIDIC PROTEIN AND NEUROFILAMENT LIGHT AS BIOMARKERS OF ACUTE SPINAL CORD INJURY

AUTHORS

Horlick, Zoe L.[1], Morelli, Tessa[2,] Stukas, Sophie[2], Gee, Cameron M.[1,3], Tsang, Angela[4], McKenzie, Miko[4], Belanger, Lise[4], Ritchie, Leanna[4], Ailon, Tamir[5], Dandurand, Charlotte[5], Paquette, Scott[5], Charest-Morin, Raphaële[3], Dea, Nicolas[5], Street, John[3], Fisher, Charles G.[3], Wilson, Jefferson[6], DiGiorgio, Anthony[7], Mac-Thiong, Jean-Marc[8], Christie, Sean[9], Wilson, Jamie[10,11], Ricks, Christian[1,2], Okonkwo, David[1,3], Kwon, Brian K.[1,3]

AFFILIATIONS

[1]International Collaboration on Repair Discoveries (ICORD), Faculty of Medicine, University of British Columbia, Vancouver, BC, Canada, [2]Department of Pathology and Laboratory Medicine, Djavad Mowafaghian Centre for Brain Health, University of British Columbia, Vancouver, BC, Canada, [3]Department of Orthopaedics, Faculty of Medicine, University of British Columbia, Vancouver, BC, Canada, [4]Vancouver Spine Research Program, Vancouver General Hospital, Vancouver, BC, Canada, [5]Division of Neurosurgery, Department of Surgery, Faculty of Medicine, University of British Columbia, Vancouver, BC, Canada, [6]Department of Neurosurgery, University of Toronto, Toronto, ON, Canada, [7]Department of Neurological Surgery, University of California San Francisco, San Francisco, CA, USA, [8]Faculty of Medicine, University of Montreal, Montreal, QC, Canada, [9]Division of Neurosurgery, Dalhousie University, Halifax, NS, Canada, [10]Department of Neurosurgery, University of Nebraska, Lincoln, NE, USA, [11]Medical University of South Carolina, Charleston, SC, USA, [12]Department of Neurosurgery, University of New Mexico, Albuquerque, NM, USA, [13]Department of Neurological Surgery, University of Pittsburgh, Pittsburgh, PA, USA

ABSTRACT

Background/objectives: Traumatic spinal cord injury (SCI) is heterogenous in terms of the population affected, presenting injury, and potential for recovery. Current measures of neurological injury rely on a complex clinical examination with significant limitations. Previous studies have identified glial fibrillary acidic protein (GFAP) and neurofilament light (NF-L) as objective classifiers of injury severity and predictors of neurologic outcome in SCI. The objective of this study was to measure and validate these serum biomarkers to further evaluate their diagnostic and prognostic utility in acute SCI.

Methods: This prospective, single-arm, multicenter clinical trial enrolled adult patients with acute traumatic SCI across eight North American sites. Serum samples were collected on days 1-7 and at 3, 6, and 12 months post-injury. GFAP and NF-L concentrations were quantified using Simoa technology. Neurological assessments established the ASIA Impairment Scale (AIS) grade and motor score at enrollment and 6 months post-injury.

Results: 58 participants with acute SCI (36 AIS A, 9 AIS B, and 13 AIS C) were enrolled, with 43 completing 6-month follow up. Temporal analysis demonstrated expected biomarker kinetics, with NF-L levels increasing progressively over the first 7 days post-injury, while GFAP peaked early and subsequently declined. Both biomarkers remained elevated relative to historical controls up to 6-12 months post-injury. Consistent with prior studies, both NF-L and GFAP levels were significantly associated with injury severity. Differences were most pronounced between AIS A and C across acute timepoints, with larger magnitude differences observed for GFAP. Serum NF-L levels differed significantly between AIS A and AIS C at all acute timepoints, with no significant differences observed between AIS A vs B or B vs C. GFAP showed significant differences between AIS A and C at days 1-4, and between AIS A vs C and AIS A vs B at days 5-7. When stratified by 6-month motor outcome (motor complete AIS A/B vs motor incomplete AIS C/D), acute NF-L (1.5–3-fold) and GFAP (4–10-fold) concentrations were significantly higher in patients who remained motor complete. Group differences were greatest at earlier timepoints and decreased over time for NF-L, while GFAP showed more consistent separation across time.

Conclusions: These findings reproduce key observations from prior work and extend them by characterizing biomarker performance across later acute and chronic timepoints. Notably, days 5-7 demonstrated improved discrimination between injury severity groups. These results support the utility of GFAP and NF-L as biomarkers of injury severity and predictors of neurological outcome in acute SCI.

#40

CHRISTOPHER KIM

MSc student · Supervisor: **Dr. James Lan**

NOBLE 69

TITLE

ADVANCING THE DIAGNOSIS OF MICROVASCULAR INFLAMMATION IN KIDNEY TRANSPLANTATION

AUTHORS

Kim, Christopher[1,2], Bissonnette, Mei Lin[1,3], Martin, Spencer[4], Cheung, Honor[4], Sherwood, Karen[1,2], Keown, Paul[1,2,3], Huntsman, David[1,4], Lan, James[1,2,3]

AFFILIATIONS

[1] Department of Pathology and Laboratory Medicine, The University of British Columbia, Vancouver, BC, Canada; [2] Vancouver General Hospital Immunology Laboratory, Vancouver Coastal Health, Vancouver, BC, Canada; [3] Division of Nephrology, The University of British Columbia, Vancouver, BC, Canada; [4] Molecular and Advanced Pathology Core, The University of British Columbia, Vancouver, BC, Canada

ABSTRACT

Background: End-stage renal disease (ESRD) affects over 50000 Canadians, significantly increasing mortality. Kidney transplantation is the preferred treatment for ESRD patients as it increases quality of life and prolongs life. Yet alloimmune injury due to microvascular inflammation (MVI) is a major contributor to long-term allograft loss. Historically, MVI has been a hallmark of antibody-mediated rejection (AMR), which is diagnosed by the detection of donor-specific antibodies (DSA) with or without C4d deposition. Recently, however, MVI in the absence of both DSA and C4d is recognized by the updated Banff 2022 classification system as a new phenotype that is common and associated with a poor prognosis. Etiology, mechanisms, and primary effector cells of this phenotype are unclear and may be alloimmune or non-alloimmune mediated, hampering accurate diagnosis and treatment. The **hypothesis** is that NK cells are the primary effector cells of alloimmune-mediated MVI, and their localization to MVI lesions may be visualized using single-cell protein imaging. The overarching aim of this project is to determine the immune profile of MVI, DSA (-), and C4d (-) through the application of single-cell spatial imaging and immunogenetics testing.

Methods: Aim (1) Creating and optimizing a panel of antibodies for cell phenotyping and tissue segmentation for the Cell DIVE multiplex immunofluorescence platform. We will analyze and compare Cell DIVE results from kidney biopsies with MVI, DSA (-), and C4d (-) to controls without rejection, AMR and the other form of alloimmune rejection called T-cell mediated rejection in the absence of MVI. Characterizing the principal effector cells of MVI related to different etiologies and their interaction with different renal tissue compartments.

Aim (2) Human leukocyte antigen (HLA) typing and DSA data will be obtained from the BC Provincial Immunology Laboratory. Non-HLA antibodies will be determined using endothelial cell crossmatch testing. Recipient KIR genotyping will be performed using real-time PCR (LinkSeq). Whereafter, interactions between donor HLA ligands and recipient NK killer immunoglobulin-like receptor (KIR) genotypes will be analyzed to evaluate the presence/absence of missing self, the inability of donor endothelial cells to provide HLA I-mediated signals to inhibitory KIRs on recipient natural killer cells.

Results: Preliminary runs of Cell DIVE have been performed on 0-hour renal biopsy and tonsil to optimize and validate antibodies (n=29) that mark renal cells and immune cells, respectively. Specific renal compartments, including glomeruli, collecting ducts, microvasculature, and distal and proximal tubules, have been visualized. All immune cells possibly involved in allograft rejection have been marked, including lymphocytes (T, B, plasma and NK cells), neutrophils, monocytes and macrophages.

Conclusions: These findings support a proteomic approach to visualize renal biopsies on a single-cell resolution. The optimized panel of antibodies will be further run as the next step on controls and test tissue to differentiate the spatial immune landscape of MVI, DSA (-), and C4d (-).

#41

BOB LIN

MSc student · Supervisor: **Dr. Honglin Luo**

NOBLE 70

TITLE

UNDERSTANDING THE MECHANISM BEHIND COXSACKIEVIRUS-INDUCED NON-CANONICAL AUTOPHAGY: IMPLICATIONS FOR AMYOTROPHIC LATERAL SCLEROSIS PATHOLOGY

AUTHORS

Lin, Bob[1,2], Luo, Honglin[1,2]

AFFILIATIONS

Pathology and Laboratory Medicine, University of British Columbia, Vancouver, BC [1]; Center for Heart Lung Innovation, St. Paul's Hospital, Vancouver, BC [2]

ABSTRACT

Background/objectives: Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease with no known cause in ~95% of cases. In ~97% of all cases, ALS is characterized by TDP-43 accumulation and mislocalization. Notably, similar TDP-43 pathology has been observed in mice infected with the positive-sense RNA enterovirus Coxsackievirus B3 (CVB3). CVB3 induces this protein mislocalization by hijacking the host autophagy pathway, which normally regulates protein and organelle turnover. During CVB3 infection, a non-canonical form of autophagy is activated that requires phosphatidylinositol 4-phosphate (PI4P) to function. However, the mechanism linking PI4P to autophagosome formation remains unclear. Based on preliminary data and literature analysis, Sorting nexin 6 (SNX6) and Acyl-CoA binding domain containing 3 (ACBD3) emerged as promising candidate mediators, potentially connecting PI4P to downstream autophagic machinery. The objective of this project is to investigate the roles of SNX6 and ACBD3 in CVB3-induced non-canonical autophagy and how they affect CVB3 viral replication.

Methods: HeLa, HEK293, and SH-SY5Y cells were transfected with siRNAs or plasmids prior to CVB3 infection. SNX6 cleavage during infection was assessed by Western blot and in vitro cleavage assays using purified CVB3 3C protease and recombinant SNX6 constructs to identify cleavage sites. The roles of SNX6 and ACBD3 in viral replication were examined using siRNA knockdown followed by infection. Viral replication was quantified by TCID50 assays (viral titer), RT-qPCR (viral RNA), and Western blot analysis of viral VP1 protein. LC3 lipidation was measured by immunoblotting to assess effects on CVB3-induced non-canonical autophagy.

Results: CVB3 infection induced the SNX6 cleavage, which was mapped to the Q27–S28 site by in vitro 3C protease assays. ACBD3 knockdown in CVB3-infected cells resulted in a ~3-fold decrease in viral VP1 protein in HEK293 and SH-SY5Y cells, a ~10-fold reduction in viral titer in both HeLa and SH-SY5Y cells, and a ~5-fold decrease in viral RNA in both HEK293 and SH-SY5Y cells. Preliminary immunoblot analyses showed that the knockdown of either SNX6 or ACBD3 reduced LC3 lipidation during CVB3 infection.

Conclusions: These findings suggest that ACBD3 plays an important pro-viral role during CVB3 infection and may contribute to CVB3-induced non-canonical autophagy. SNX6 was identified as a substrate of the viral 3C protease and may participate in this pathway, though its role in viral replication appears limited. Ongoing studies aim to further define the mechanisms linking ACBD3 and SNX6 to PI4P-dependent non-canonical autophagy during CVB3 infection.

#42

ADAM MCGIVERN

MSc student · Supervisor: **Dr. James Lan**

NOBLE 71

TITLE

IMPLEMENTATION AND ASSESSMENT OF DECENTRALIZED DONOR-DERIVED CELL-FREE DNA TESTING FOR KIDNEY TRANSPLANT MONITORING IN CANADA

AUTHORS

McGivern, Adam [1,2], Fenninger, Franz, [1,2], Xu, Rulan [2], Sherwood, Karen [1,2], Keown, Paul [1,2,3], Lan, James [1,2,3]

AFFILIATIONS

[1] Department of Pathology and Laboratory Medicine, University of British Colombia, Vancouver, BC, Canada; [2] Vancouver General Hospital Immunology Laboratory, Vancouver Coastal Health, Vancouver, BC, Canada; [3] Division of Nephrology, Faculty of Medicine, University of British Colombia, Vancouver, BC, Canada

ABSTRACT

Background: Of the many Canadians (1 in 10) with chronic kidney disease, many will require a kidney transplant. However, despite the serious and foreseeable risk of transplant rejection, standard clinical practice lacks adequate monitoring tools for kidney health. For example, while serum creatinine is a ubiquitous test used to estimate kidney function, it is a late marker of injury. This leads to missed treatment opportunities. Though biopsy remains the gold standard assessment, it is deterrently invasive. Overall, this engenders poor health outcomes for allograft recipients, which in turn exacerbates healthcare system stress. Recently, donor derived cell-free DNA (dd-cfDNA) has emerged as a non-invasive and early indicator of kidney allograft injury. This test analyzes the amount of DNA released from cells of the transplant (genetically distinct from recipient cells' DNA), with high proportions suggesting rejection. Though promising, it faces barriers to reaching Canadian patients. Chiefly, it remains centralized to US laboratories, making it time and cost-prohibitive for Canadians – especially those in remote areas. A decentralized model may be the key to overcoming such barriers and increasing test accessibility for Canadians. Here, our objective is to address the current lack of information about decentralized cfDNA performance in a Canadian context. We hypothesize that a decentralized model of cfDNA testing will achieve comparable test performance to that of CareDx's central model.

Methods: Blood will be drawn from various cohorts of transplant patients at Vancouver General Hospital (VGH). An Illumina MiSeq Sequencing System, which uses single nucleotide polymorphisms to discriminate between donor and recipient DNA, will be used to measure the proportion of dd-cfDNA in the blood. Samples will be tested concurrently by our industry partner, CareDx.

Aim 1: Determine the analytic validity of dd-cfDNA testing in British Columbia. To identify pre-analytic sources of variation in test results, blood from transplant recipient cohorts at VGH will be tested. We will analyze whether different methods of cfDNA extraction (n=10) and storage (n=10) bear upon test results.

Aim 2: determine the clinical validity of dd-cfDNA testing in BC. To clarify baseline test results, cfDNA testing will be performed on 20 stable transplant patients at VGH. To clarify the threshold for diagnosing injury, 100 biopsy-due patients will be cfDNA tested, and their results correlated with the biopsy's.

Results: for aim 1, our lab has obtained preliminary results suggesting that, between two common commercial storage tubes (PAXgene & STRECK), the latter sees less genomic DNA contamination after multiple days. For aim 2, currently underway, we expect to see agreement between our test results and CareDx's, and correlation with patient biopsies.

Conclusions: results already obtained, and expected results, will clarify the ambiguities around decentralized dd-cfDNA test protocol and confirm the model's viability in Canada. Next steps will be evaluating real-world test performance by launching it for clinical use, as well as cost-benefit analyses.

#43

NINA REECE

MSc student · Supervisor: **Dr. Ying Wang**

TITLE

EVALUATING THE THERAPEUTIC POTENTIAL OF FUCOIDAN FOR COATING DRUG-ELUTING STENTS

AUTHORS

Reece, Nina[1,2], Buenaventura, Gaea[1,2], Chatha, Aakar[1,2], Ho, Vivian[1,2], Elishaev, Maria[1,2], Cheng, Wan-Hei[1,2], Leung, Samuel[1,2], Sun, Tao[1,2], Kong, Hyejin Julia[1,2], Wang, Ying[1,2]

AFFILIATIONS

[1]Department of Pathology and Laboratory Medicine, University of British Columbia, Vancouver, BC, Canada, [2]Centre for Heart Lung Innovation, St. Paul's Hospital, Vancouver, BC, Canada

ABSTRACT

Background/Objectives: Percutaneous coronary intervention (PCI, or the insertion of a stent) is widely used to treat coronary artery disease, yet in-stent restenosis (re-narrowing of the artery) still occurs in about 12% of patients. More than 2 million PCI procedures are performed annually, and these patients may require repeat PCI or even open-heart surgery to treat restenosis. Restenosis results from smooth muscle cell (SMC) overgrowth and delayed endothelial healing following stent implantation. Current stents are coated with drugs, known as drug-eluting stents (DES), and employ mTOR inhibitors such as everolimus to non-specifically inhibit SMC and endothelial cell (EC) proliferation and thereby reduce restenosis, but these inhibitors also suppress endothelial healing. Therefore, improving the design of DES to promote early endothelialization while inhibiting SMC proliferation is essential for improving post-PCI patient outcomes.

Fucoidan is a sulfated polysaccharide that can be extracted from brown algae. Previous literatures have shown that fucoidan improved the formation of the EC barrier when coated on a vascular graft in a rabbit model. It also inhibited proliferation of human vascular SMCs, suggesting that fucoidan may have cell-specific effects. We hypothesize that fucoidan will inhibit early in-stent restenosis following PCI by facilitating re-endothelialization and reducing SMC proliferation.

Method: To determine the cell-specific actions of fucoidan on pro-restenosis and pro-healing processes, human coronary artery ECs (HCAEC) and human coronary artery SMCs (HCASMC) will be exposed to 0-10 ug/mL fucoidan and assessed for viability, migration, inflammation, and proliferation using confocal microscopy and flow cytometry. Fluorescence-labeled fucoidan will be used to determine whether fucoidan preferentially binds to ECs or SMCs. The study will also assess whether fucoidan selectively activates pro-healing signaling pathways in ECs while inhibiting proliferation-associated pathways in SMCs. HCAECs and HCASMCs will be treated with the same dose of fucoidan, and bulk RNA sequencing, western blot, and confocal microscopy will be employed to determine the activities of the PI3K/AKT/mTOR, NF-kB, and p38 MAPK pathways targeted by fucoidan.

Results: Low-dose fucoidan did not affect cell viability in either cell type, supporting that the observed pro-healing effects arise from selective uptake or differential signaling rather than cytotoxicity. HCASMC proliferation decreased in a dose-dependent manner, whereas the proliferation of HCAECs remained unchanged from 0-5 ug/mL and increased by approximately 20% at 10 ug/mL fucoidan.

Conclusions: These findings confirm that fucoidan's effects are not driven by cytotoxicity. Instead, the selective inhibition of HCASMCs and increased growth of HCAECs reflects true biological specificity rather than non-specific toxicity. Future work will focus on testing the pro-healing effects of fucoidan in a novel 3D co-culture PCI injury model.

#44

WILLIE WU

MSc student · Supervisor: **Dr. Katey Enfield & Dr. Martial Guillaud**

TITLE

DISSECTING TUMOR MICROENVIRONMENT ARCHITECTURE THROUGH SPATIAL ANALYSIS IN EARLY-STAGE NON-SMALL CELL LUNG CANCER

AUTHORS

Wu, Willie[1,2]; Anderson, Wyatt[1,3]; Inaba, Fumiya[1,2]; Gallagher, Paul[1]; Noureddine, Kouther[1]; Fitzsimons, Evelyn[1]; Xiang, Richard[4]; Martin, Spencer[3]; McGuire, Anna[4]; Guillaud, Martial[1,2,3]; MacAulay, Calum[1,2,3]; Enfield, Katey[1,2,3]

AFFILIATIONS

[1] Department of Basic and Translational Research, BC Cancer Research Institute, Vancouver, BC, Canada; [2] Interdisciplinary Oncology Program, University of British Columbia, Vancouver, BC, Canada; [3] Department of Pathology and Laboratory Medicine, University of British Columbia, Vancouver, BC, Canada; [4] Department of Surgery, University of British Columbia, Vancouver, BC, Canada

ABSTRACT

Background/Objectives: Lung cancer is the leading cause of cancer-related mortality worldwide, with non–small cell lung cancer (NSCLC) being the most common subtype and having a 5-year survival rate below 20%. Immune checkpoint inhibitors (ICIs) targeting the PD-1/PD-L1 axis have transformed NSCLC treatment by reinvigorating T cell–mediated anti-tumor immunity. Current patient selection for adjuvant ICIs based on PD-L1 expression on tumor cells, as determined by single-marker immunohistochemistry, provides limited predictive accuracy. Emerging studies show that never-smokers with high PD-L1 experience markedly poorer ICI responses compared to ever-smokers, revealing a biological gap in current biomarkers that overlook the spatial architecture of the tumor microenvironment (TME). Recent advances in multiplex imaging now enable simultaneous detection of 40+ protein markers within a single tissue section, achieving unprecedented resolution. Our project aims to characterize the TME of ever- and never-smokers in early-stage NSCLC using multiplex imaging and spatial analysis, focusing on how smoking history and histologic growth pattern shape this ecosystem. We hypothesize that spatial TME features will better capture biologically meaningful differences between ever- and never-smokers than PD-L1 expression alone and will reveal candidate multicellular architectures that may underlie ICI sensitivity in a subset of never-smokers.

Methods: 88 treatment-naïve NSCLC patients (56 ever-smokers, 32 never-smokers) contributed 176 tumor samples. Multiplex imaging with an optimized 14-plex panel profiled immune, stromal, and tumor lineages. A machine learning pipeline segmented cells and probabilistically assigned phenotypes, including $CD4^+$, $CD8^+$, $PD\text{-}1^+$ $CD8^+$ T cells, B cells, macrophages, natural killer cells, epithelial cells, $PD\text{-}L1^+$ tumor cells, and stromal cells. Spatial organization was analyzed with cell-cell pairwise interactions and cellular neighborhood graphs, correlating spatial features with histology, smoking status, and relevant clinical features.

Results: Over 450,000 cells were confidently classified into 10 phenotypes with the new machine learning pipeline. Cell phenotypes were mapped back onto fluorescent images for visual inspection, showing fewer unassigned cells and improved cell type annotation accuracy compared to results from the standard unsupervised clustering approaches. In lung adenocarcinoma, tumors with micropapillary subtypes from ever-smokers exhibited enriched $CD4^+$, $CD8^+$, and B cell neighborhoods compared to never-smokers. Among never-smokers, the proportions of adaptive immune cells varied by histologic subtype, whereas innate populations remained similar.

Conclusions: Spatial TME analysis reveals smoking-dependent architectures beyond PD-L1 expression that may refine ICI stratification and inform biomarker development in NSCLC.

#45

FATIMA YASEEN

MSc student · Supervisor: **Dr. Helene Cote and Dr. Melanie Murray**

NOBLE 72

TITLE

EXAMINING DIFFERENCES IN BLOOD MITOCHONDRIAL DNA CONTENT BETWEEN WOMEN LIVING WITH AND WITHOUT HIV IN THE 2021-2025 ANTIRETROVIRAL THERAPY ERA FROM BRITISH COLUMBIA.

AUTHORS

Yaseen, Fatima[1], Kowatsch, Monika M.[2,3,4], Povshedna, Tetiana[1,6,7], Gadawska, Izabelle[1], Tognazzini, Shelly[5], Kaida, Angela[2,3,5], King, Elizabeth M.[2,3,4,5,8], Cote, Helene C.F.[1,2,3,6,7], Murray, Melanie C.M.[2,3,4,7,8] on behalf of the British Columbia CARMA-CHIWOS Collaboration (BCC[3]; CIHR CTN+335)

AFFILIATIONS

[1] Department of Pathology and Laboratory Medicine, The University of British Columbia; [2] Women's Health Research Institute, British Columbia Women's Hospital and Health Centre; [3] CIHR Pan-Canadian Network for HIV and STBBI Clinical Trials Research (CTN+); [4] Department of Medicine, University of British Columbia; [5] Faculty of Health Sciences, Simon Fraser University; [6] Centre for Blood Research, University of British Columbia; [7] Edwin S.H. Leong Healthy Aging Program, University of British Columbia, Vancouver; [8] Oak Tree Clinic, British Columbia Women's Hospital and Health Centre

ABSTRACT

Introduction: Women living with HIV have shorter life and health spans compared to women without HIV. Declines in mitochondrial DNA (mtDNA) content is a marker for aging. Previous studies show that women living with HIV have lower blood mitochondrial DNA (mtDNA) content than women without HIV. MtDNA content can be altered by both HIV and its treatments, particularly earlier nucleoside reverse transcriptase inhibitors (NRTIs) such as zidovudine (AZT) and other dideoxynucleosides that can cause chain termination within replicating mtDNA. These early treatments were phased out in the mid-2000s and less is known about the effects on mtDNA content from current NRTIs. Here, we investigate the mtDNA content in a contemporary cohort of women living with and without HIV. We hypothesize that declines in mtDNA content could in part explain the increased health and age-related disparities observed in women living with HIV.

Methods: Participants in this cross-sectional study are from the BCC3 cohort, a holistic community-based study of healthy aging in 652 women including 309 living with HIV and 343 living without HIV in British Columbia. Blood mtDNA content was measured using a monochrome multiplex qPCR assay and reported as the mtDNA/nDNA ratio. Comparisons between groups were done using Chi-squared or Mann-Whitney tests.

Results: We measured mtDNA content in 188 women living with (88% undetectable HIV viral loads) and 300 without HIV. Both groups were similar with respect to age (median [IQR] 47 [39-54] years and 44 [32-56] years), body mass index, smoking, and opioid use. MtDNA content was slightly higher in women with HIV 162 [135-183] vs. without HIV 154 [129-178], p=0.042.

Conclusions: These preliminary results suggest that mtDNA content for women living with HIV is not lower than women without HIV. An explanation for this could be that our participants are socio-demographically similar and in the 2020's HIV treatment era where medications may be more mitochondria-friendly. Following assay completion for all participants, multivariable analysis will investigate factors associated with mtDNA, adjusting for potential confounders.

#46

VIVIAN ZHU

MSc student · Supervisor: **Jacqueline Quandt**

TITLE

THE MULTIPLE SCLEROSIS-ASSOCIATED NR1H3 ARG413GLN MUTATION ALTERS ACUTE MYELOID RESPONSES AND REVEALS STAGE-DEPENDENT CENTRAL NERVOUS SYSTEM IMMUNE REMODELING IN EXPERIMENTAL AUTOIMMUNE ENCEPHALOMYELITIS

AUTHORS

Zhu, Vivian[1]; Kamma, Emily[1]; Becquart, Pierre[1]; Farhangi, Sahar [1]; Wong, Curtis [1]; Tharakan, Robin[1]; Vilariño-Güel, Carles [1,2]; Quandt, Jacqueline[1]

AFFILIATIONS

[1]Department of Pathology and Laboratory Medicine, University of British Columbia, Vancouver, BC, Canada; [2]Department of Medical Genetics, University of British Columbia, Vancouver, BC, Canada.

ABSTRACT

Background/objectives: Progressive multiple sclerosis (MS) lacks models that recapitulate disease progression. We generated mice harbouring a mutation in nuclear receptor subfamily 1 group H member 3 (Nr1h3) Arg413Gln, homologous to the human Nr1h3 R415Q variant identified in heterozygous individuals with MS from high-incidence families. Nr1h3 encodes Liver X Receptor alpha, a transcriptional regulator of reverse cholesterol transport and lipid homeostasis. Mutant mice exhibited reduced reparative markers in myeloid populations, worsened disability, demyelination, and axonal damage, and failed recovery following experimental autoimmune encephalomyelitis (EAE), a widely used mouse model of MS. We aimed to determine whether this mutation alters myeloid phenotypes across disease stages.

Methods: Myelin oligodendrocyte glycoprotein 35–55 EAE was induced in female mice. CNS immune populations were analyzed by flow cytometry at peak (day 18) and chronic (day 50) disease stages.

Results: At peak EAE, total infiltrate and microglia numbers were comparable between genotypes in spinal cord and brain. In spinal cord, T and B cell numbers and proportions were unchanged, yet HET mice showed a higher proportion of CD11c+ monocyte-derived macrophages (73.3%±8.0 vs 63.0%±2.8; p=0.03) and reduced CD163 (reparative marker) in myeloid dendritic cells (5.2±0.34 vs 5.8±0.41 $\times 10^3$; p=0.04). In brain, despite comparable infiltrate and microglia numbers between genotypes, HET mice exhibited higher T and B cell numbers ($p<0.05$) and increased CD11c+ microglial counts (0.32±0.05 vs 0.22±0.07 $\times 10^6$; p=0.03). At the chronic stage, resolution of inflammation was reflected by a marked reduction in total CD45+ cells in spinal cord, although the proportions of myeloid dendritic cells and T cells were increased ($p<0.01$). In chronic brain, absolute infiltrates (including T cells) and microglia, particularly CD11c+ microglia, were reduced compared to peak disease; however, T cells were proportionally enriched ($p<0.05$). Notably, infiltrate composition and CD163 expression were similar across genotypes in chronic spinal cord and brain.

Conclusions: Nr1h3 Arg413Gln mutation effects are most pronounced in early myeloid and microglial phenotypes related to repair/immune resolution and warrant further investigation for their impact on subsequent progression and recovery.

#47

CINDY SHI

MSc student

TITLE

AORTIC ROOT FUNCTIONAL ANATOMY FOR TRANSCATHETER AORTIC VALVE REPLACEMENT: A CADAVERIC STUDY

AUTHORS

Cindy Shi, Majid Alimohammadi

ABSTRACT

Background/objectives:

Complications after Transcatheter Aortic Valve Replacement (TAVR) such as coronary obstruction, conduction system disturbances, and aortic injury are associated with high mortality and known to vary by geographic region.

Native anatomical criteria remain central to early risk stratification. Characterizing the baseline distribution of these anatomical features may inform TAVR risk assessment as the procedure expands to broader and lower-risk patient groups.

Methods:

Morphometric analysis of 50 formalin-fixed cadavers. Precise measurements of cusp height, coronary ostia height, sinus of Valsalva dimensions, membranous septum length, presence of mitral stenosis, sinus depth, annular perimeter, and sinotubular junction will be taken in specimens. These physical measurements will be compared against established clinical risk thresholds for coronary obstruction and conductive system disturbance derived from computed tomography (CT) and registry data.

Results:

Characterization of the frequency of potentially high-risk anatomy (e.g., cusp height > coronary height) within the local cohort.

Identification of the co-occurrence of specific anatomical characteristics, such as a short membranous septum length (<4.7 mm)—which determines the safe extent of device penetration—and the presence of the mitral stenosis within the aortic root wall (found in 40% of cases), which increases the risk of iatrogenic rupture and conduction blocks.

Conclusions:

Physical anatomical measurements provide a baseline for TAVR planning that accounts for population-specific variability. By characterizing native structural relationships independent of valve simulations, this work supplements current CT frameworks and helps refine the understanding of risk for a broad range of procedural complications.

#48

ISABELLA DIBERARDINO

MSc student · Supervisor: **Dr. Cheryl Wellington**

TITLE

DEFINING POPULATION REFERENCE INTERVALS FOR PLASMA BRAIN-DERIVED TAU AND PHOSPHORYLATED-TAU-217 ACROSS THE LIFESPAN

AUTHORS

DiBerardino, Isabella[1]; Cooper, Jennifer[2]; Stukas, Sophie[2]; Karikari, Thomas[3,4]; Hutchison, Jamie[5]; Wang, Kevin[6]; Kobeissy, Firas[6]; Mondello, Stefania[7]; Diaz-Arrastia, Ramon[8]; Puccio, Ava[9]; Wellington, Cheryl[2,10,11]

AFFILIATIONS

[1]Department of Neuroscience, Djavad Mowafaghian Centre for Brain Health, Faculty of Medicine, University of British Columbia, Vancouver, BC, Canada, [2]Department of Pathology and Laboratory Medicine, Djavad Mowafaghian Centre for Brain Health, Faculty of Medicine, University of British Columbia, Vancouver, BC, Canada, [3]Alzheimer's Disease Research Center, University of Pittsburgh, Pittsburgh PA, USA, [4]Biofluid Biomarker Laboratory, Western Psychiatric Hospital, University of Pittsburgh Medical Center, Pittsburgh PA, USA, [5]Children's Hospital of Eastern Ontario, Ottawa, ON, Canada, [6]Department of Neurobiology, Morehouse School of Medicine, Atlanta, GA, USA, [7]Department of Biomedical and Dental Sciences and Morphofunctional Imaging, University of Messina, Messina, Italy, [8]Department of Neurology, University of Pennsylvania, Philadelphia, PA, USA, [9]Department of Neurological Surgery, School of Medicine, University of Pittsburgh Medical Center, Pittsburgh, PA, USA, [1,0]International Collaboration on Repair Discoveries, Vancouver, BC, Canada, [1,1]School of Biomedical Engineering, University of British Columbia, Vancouver, BC, Canada

ABSTRACT

Background: Blood-based brain-derived biomarkers are increasingly recognized as powerful tools for screening, diagnosis, prognostication, and disease monitoring across a range of neurological disorders. Plasma phosphorylated tau-217 (p-tau-217) has emerged as a leading biomarker associated with amyloid pathology in Alzheimer's disease (AD). Although ultrasensitive assays for p-tau isoforms have been widely evaluated in neurodegenerative diseases, studies of brain-derived (BD)-Tau are limited, and its release kinetics, relationship to injury severity, and clinical outcomes remain unclear. Establishing reference intervals (RI) to discriminate normal from abnormal values is an essential step in the validation and eventual implementation of clinical biochemical laboratory tests. We therefore developed RIs for these two biomarkers.

Methods: 2500 plasma samples from male and female participants aged 3-79 years old were analyzed for concentrations of BD-Tau and p-tau-217 to create RIs. Samples were obtained from the Canadian Health Measures Survey (CHMS), a national study that collects demographics, health questionnaires, clinical data, and biospecimens from participants. Analysis was performed on the Quanterix Simoa HD-X analyzer using the BD-Tau Advantage Plus and ALZpath p-tau-217 Advantage Plus assay. Discrete and continuous RIs will be produced for each biomarker. Discrete RIs are produced according to the Clinical Laboratory Standards Institute guidelines (EP28-A3c) using the 2.5th and 97.5th percentiles of each bin. Continuous RIs are created using generalized additive models for location, scale, and shape (GAMLSS) using the 5th and 95th percentiles. We will also examine the influence of demographic, health, and laboratory factors on BD-Tau and p-tau-217 concentrations, including age, sex, body mass index (BMI), and kidney function.

Results: After analysis, age partitions for discrete RIs will be created, resulting in two to five age-bins per biomarker which reference intervals were generated for. Continuous RIs will describe smooth centile curves across all ages, from which point estimates for any age can be calculated. In addition to the percentiles that are used as RIs, additional percentiles will be extracted to provide reference curves. *Data analysis is in progress.*

Conclusions: Both discrete and continuous RIs for plasma BD-Tau and p-tau-217 may help refine normative cut offs for each biomarker across the lifespan.

#49

CRAIG IVANY

PhD student · Supervisor: **LUCY PERRONE**

TITLE

UNDERSTANDING WHAT SHAPES CHANGE IN LABORATORY SYSTEMS: A STRUCTURED APPROACH

AUTHORS

Ivany[1], Craig, Dr. Kalua[2], Khumbo, Dr. Perrone[1], Lucy

AFFILIATIONS

[1]UBC Department of Pathology and Laboratory Medicine; [2]UBC School of Population and Public Health

ABSTRACT

Background

Laboratory medicine and pathology (LMP) services constitute critical yet structurally complex health system infrastructure. In British Columbia (BC), laboratory services operate as an independent meso-level system within broader political and regulatory environments and are delivered through a hybrid public–private network. Despite sustained policy efforts to advance system integration, implementation of system-level interventions has been uneven. Implementation science identifies context as a decisive influence on outcomes; however, context remains variably defined, inconsistently examined, and often under-specified in large, multi-level interventions. This ambiguity is particularly salient in laboratory medicine, where governance, legislation, funding, and digital infrastructure intersect. A structured, theory-informed approach to contextual analysis is therefore required. This study develops and demonstrates a structured contextual determinant methodology for analyzing complex laboratory system interventions using the BC LMP system as a case-informed example.

Materials & Methods

Method development was guided by the Basel Approach for Contextual Analysis, providing structure for theoretical framing, empirical characterization, and reporting. The Consolidated Framework for Implementation Research (CFIR) was adopted as the determinant backbone, organizing context across inner setting, outer setting, and individual actor domains. The Implementation in Context (ICON) framework refined domain specification, while Watson's work on external context strengthened delineation of system-level influences. To deepen analysis of the CFIR individual actor domain, a constructivist-informed perspective (Mielke, 2022) was applied to examine how actors interpret contextual conditions. These refinements were integrated within CFIR, preserving its structure while enhancing specification. Empirical characterization was conducted through structured review of policy documents, legislation, and system-level reports, supported by qualitative synthesis to identify implementation-relevant determinants. This establishes a foundation for subsequent analysis of how actors interpret and mobilize context.

Results

Application of the methodology to the BC LMP system demonstrates analytic feasibility and coherence. Provisional classification identified determinants across macro, meso, and micro levels. The approach provides an explicit pathway linking contextual characterization to implementation-relevant determinants, reducing reliance on implicit or post hoc explanations.

Conclusion

This work establishes a methodological foundation for contextual analysis in complex laboratory systems. By integrating CFIR with contemporary contextual frameworks and a constructivist-informed perspective, the approach strengthens clarity and rigour. Future research will examine determinant salience, interaction, and temporal dynamics, and assess how context-informed strategies influence system-level integration. The methodology supports evaluation, policy development, and implementation planning in laboratory medicine.

#50

MICHAEL LANE

PhD student · Supervisor: **David Granville**

TITLE

EXTRACELLULAR GRANZYME B DRIVES COORDINATED TRANSCRIPTIONAL REPROGRAMMING IN HUMAN KERATINOCYTES

AUTHORS

Lane Michael[1,2,3], Aubert Alexandre[1,2,3], Prudova Anna[1,2,3], Tang Jeffrey[4,5,6], Jung Karen[1,2,3], Granville David[1,2,3,5,6]

AFFILIATIONS

[1]Department of Pathology and Laboratory Medicine, University of British Columbia, Vancouver, BC, Canada; [2]International Collaboration on Repair Discoveries (ICORD), University of British Columbia, Vancouver, BC, Canada; [3]British Columbia Professional Firefighters' Burn and Wound Healing Group, Vancouver Coastal Health Research Institute, University of British Columbia, Vancouver, BC, Canada.; [4]Department of Anesthesiology, Pharmacology and Therapeutics, The University of British Columbia; [5]Centre for Heart Lung Innovation, Vancouver, BC, Canada; [6]Providence Research, Providence Health Care, Vancouver, BC, Canada

ABSTRACT

Background/objectives: Granzyme B (GzmB) is a serine protease elevated in chronic wounds that cleaves key extracellular matrix, cell-cell junction, and cell surface proteins, impairing tissue remodeling. Inhibition of GzmB improves wound healing and reduces scarring in preclinical models. To better understand the downstream mechanisms driven by GzmB in keratinocytes, we sought to characterize the global transcriptional response to extracellular GzmB and identify the key signaling pathways.

Methods: Human skin cells (HaCaT) were treated with 50 nM recombinant human GzmB or PBS for 6 h (n = 3/group). Differential expression was analyzed using DESeq2. Gene set enrichment analysis (fGSEA) was performed across Hallmark, KEGG, Reactome, and Gene Ontology collections with leading-edge gene identification for each significant pathway. Upstream cytokine activity was inferred using CytoSig, a transcriptome-based cytokine signaling prediction tool. A protein-protein interaction (PPI) network was constructed using STRING and visualized with hub genes identified by network degree centrality.

Results: DESeq2 identified 145 differentially expressed genes (106 upregulated, 39 downregulated; padj < 0.05, |LFC| ≥ 0.58). fGSEA revealed strong upregulation of TNFα/NF-κB signaling (NES = 2.52; leading genes: MYC, VEGFA, NR4A1, EGR1, SERPINB2), cytokine-cytokine receptor interaction (NES = 2.18; VEGFA, EGFR, IL18, MET), IL-2/STAT5 signaling (NES = 2.16; PIM1, MYC, TNFSF10), ErbB/RTK signaling (NES = 2.21; MET, HBEGF, NRG1, EGFR), and collagen binding (NES = 2.16; MMP13, THBS1, ITGA2, CD44). Oxidative phosphorylation (NES =− 2.40; CYCS, NDUFB3, COX subunits) and aerobic respiration (NES =− 2.33) were markedly suppressed, consistent with a shift toward an inflammatory, glycolytic phenotype. CytoSig upstream cytokine activity inference identified 26 significant signatures, with HGF (z = 9.7), EGF (z = 9.2), FGF2 (z = 7.0), IL-1β (z = 6.8), and VEGFA (z = 6.0) as the top activated mediators, while BMP4 (z =− 4.9) and BMP6 (z =− 4.3) were suppressed. STRING PPI network analysis restricted to the 145 DEGs (confidence ≥ 0.7) identified 35 interconnected proteins forming 32 high-confidence edges. MYC was the dominant hub with the highest degree (6 interactions within the DEG subnetwork), followed by EGR1, PTGS2 (4 each), and MET, IRS1, SERPINE1 (3 each), consistent with MYC's established role as a master transcriptional regulator.

Conclusions: Extracellular GzmB induces a coordinated transcriptional reprogramming in keratinocytes characterized by upregulation of inflammatory, growth factor, and ECM remodeling gene programs, with a transcriptional signature consistent with HGF, EGF, and IL-1β-like upstream mediator activity and with concomitant suppression of mitochondrial metabolism and BMP signaling. PPI network analysis identifies MYC, MET, EGR1, and SERPINE1 as central interaction nodes among the DEGs, positioning GzmB as a potent extracellular driver of keratinocyte inflammatory gene expression and a candidate therapeutic target in wound healing.

#51

MICHELLE LIN

PhD student · Supervisor: **Dr. Jayachandran Kizhakkedathu**

NOBLE 77

TITLE

DEVELOPING CELL SURFACE TARGETED ENZYMES FOR BLOOD GROUP CONVERSION

AUTHORS

Lin, Michelle C. Q.[1]; Hosseini, Hassan[1]; Moon, Haisle[1]; Ho, Freda[1]; Withers, Stephen G.[2]; Kizhakkedathu, Jayachandran N.[1]

AFFILIATIONS

[1]Center for Blood Research, Faculty of Medicine, Department of Pathology and Laboratory Medicine; [2]Faculty of Science, Department of Chemistry

ABSTRACT

Background/objectives:

Blood transfusions are essential in modern medicine. With over 30 known discrete blood groups defined by more than 270 antigens, the human blood group system is incredibly complex. The A and B carbohydrate antigens of the ABO blood group system are the most immunogenic and clinically significant. As such, they must be matched with careful blood typing to avoid fatalities. In emergency situations when the host blood type is unknown, the blood type O is often used, and is considered as 'universal blood'. Absent of A or B surface antigens, O-type blood will not trigger major immune responses in hosts regardless of recipient blood type. In cases of chronic transfusions (e.g. patients with thalassemia, sickle cell anemia, or myelodysplastic syndromes), the matching of several minor antigens is necessary to avoid alloimmunization. Blood matching for alloimmunized patients is challenging and demanding for the blood system. These challenges illustrate the critical need for the creation of a 'true' universal blood where blood can be transfused to patients without the fear of incompatibility.

Recent research shows that the carbohydrate-based antigens A and B that are located on the surfaces of red blood cells (RBCs) can be enzymatically converted to the universal type O blood. However, this practice has not yet been adopted clinically. More active and cell-surface specific enzymes are necessary for clinical translation. Here, we aim to develop a method to create highly active cell-surface specific enzymes capable of converting the major A carbohydrate antigen to the universal H-type antigen associated with O-type blood. We hypothesize that by conjugating A-blood group specific antibodies with A-blood cleaving enzymes, antigen cleavage efficiency on the cell surface will be enhanced.

Methods: A-blood group specific antibodies were conjugated with A-blood cleaving enzymes. Once synthesized, conjugates were validated through SDS-PAGE. Successful conjugates were then tested in A-type blood samples using flow cytometry to measure their ability to 1) bind to the A antigens on the surfaces of red blood cells and 2) convert the major A carbohydrate antigen to an H-type antigen.

Results: Preliminary data show that the antibody-enzyme conjugates were able to successfully bind to the RBC surfaces and convert the major A antigen to an H-type antigen.

Conclusions: Conjugating the A-blood cleaving enzyme to the anti-A antibody did not interfere with the ability of the antibody to bind to RBC surfaces. The conjugation reaction also does not appear to interfere with the functionality of the A-blood cleaving enzyme in converting A antigens to H-type antigens. Further studies to investigate the toxicity and biocompatibility of these antibody-enzyme conjugates will be done. Explorations on synthesizing B-blood group specific antibody-enzyme conjugates will also be conducted.

#52

ZOE LOFFT

PhD student · Supervisor: **Dr. Angela Devlin**

TITLE

HIGH FOLIC ACID IMPACTS INSULIN-PRODUCING BETA-CELL FUNCTION

AUTHORS

Lofft, Zoe[1,3], Kajino, Mayu[4], Huang, Elaine[2,3], Devlin, Angela[1-3]

AFFILIATIONS

Departments of [1]Pathology and Laboratory Medicine and [2]Pediatrics, The University of British Columbia, [3]BC Children's Hospital Research Institute, Vancouver, Canada; [4]Department of Clinical Pharmacokinetics, Kanzawa University, Japan.

ABSTRACT

Background/objectives: Many pregnant women consume 2-5x more folic acid than recommended (0.4mg/day), which may adversely affect the metabolic health of the child. The pancreas maintains the second highest folate reserves in the body. However, little is known about how folic acid impacts the pancreas during development. The suckling period is a time of interest because it represents a critical developmental window where beta-cells undergo rapid proliferation. The objective of this study is to test the hypothesis that high folic acid impairs beta-cell function.

Methods: Glucose stimulated insulin secretion (GSIS) was assessed in MIN6 cells treated (24-48h) with folic acid or methyltetrahydrofolate (MTHF). Mitochondrial respiration (Seahorse MitoStress Test), bulk RNA-seq, and folate receptor expression (FOLR1, western blotting) were also evaluated. GSIS was performed in islets from suckling C57BL6/J offspring (age 13-15 days) from dams fed a control or high folic acid diet (2 or 20mg/kg diet) for 8-12 weeks.

Results: MIN6 cells treated with high MTHF or folic acid (5-125x control) had lower GSIS ($p<0.05$) vs controls under high glucose conditions. Cells treated with high folic acid or MTHF had lower maximal mitochondrial respiration ($p=0.11$). Ninety genes ($p<0.05$) were differentially expressed, affecting pathways related to AMPK and mTOR signalling, in high MTHF-treated MIN6 cells. No effect of high folic acid on FOLR1 expression was observed. Male and female offspring from dams supplemented with high folic acid weighed less ($p<0.01$) than controls despite no differences in body weight of the dams. GSIS, under high glucose conditions, was higher ($p<0.05$) in islets from male and female offspring from high folic acid-fed dams compared to controls.

Conclusions: Acute high MTHF or folic acid treatment diminished GSIS in MIN6 cells. In contrast, maternal high folic acid enhanced GSIS in offspring islets during suckling. Our findings suggest that high folic acid impacts beta-cell function, but the effect depends on developmental stage.

#53

JOHN PERRIER

PhD student · Supervisor: **Dr. Ed Pryzdial**

TITLE

TISSUE FACTOR AND PROCOAGULANT LIPID ON DENGUE VIRUS AND HUMAN CORONAVIRUS-229E

AUTHORS

Perrier, John[1,3], West, Henry[1,3], Lin, Bryan[2,3], Sutherland, Michael[1,3,4], Pryzdial, Ed[1,3,4]

AFFILIATIONS

[1]Department of Pathology and Laboratory Medicine, [2]Department of Biochemistry and Molecular Biology, [3]Centre for Blood Research, [4]Canadian Blood Services, Medical Affairs and Innovation

ABSTRACT

Background/objectives: Numerous viruses modulate blood clotting, leading to effects on hemostasis and inflammation. Since many virus types derive a membrane envelope from host cells containing common procoagulant constituents, it is reasonable that a ubiquitous molecular basis exists. Our objective is to characterize this biochemistry and provide a unifying mechanism. Here we compared purified viruses from distinct families; dengue virus (DENV), a hemorrhagic flavivirus, and the inflammatory coronavirus 229E (HCoV-229E) largely responsible for the common cold. We have previously reported the host-encoded transmembrane coagulation initiator, tissue factor (TF), and procoagulant phospholipid (proPL) on the surface of several purified herpes viruses. Similar to DENV and HCoV-229E, these viruses are enveloped, retaining host proteins and a lipid membrane. Since TF is widely expressed on infectible cells, we hypothesize that TF is ubiquitous on enveloped viruses and influences viral pathology. The presence of TF antigen on the viral envelope, along with associated coagulation activity, will be assessed in both DENV and HCoV-229E

Methods: Purified DENV and HCoV-229E was evaluated by immunogold electron microscopy (EM) to show TF antigen. A chromogenic assay probed the TF-, proPL-, and factor (F) VIIa-dependent activation of FX to FXa. Normal plasma clotting assays were conducted using purified virus as a coagulation initiator.

Results: TF was detected on purified DENV by EM, which co-stained for virus-encoded E protein, confirming virus identity. TF was found on viral particles in HCoV-229E preparations. DENV and HCoV-229E induced dose-dependent increases in FXa generation and shortened clotting time. These activities were inhibitable by anti-TF antibody or NAPc2, which confirmed the involvement of TF function. Inhibition by lactadherin demonstrated the presence of essential proPL.

Conclusions: These data expand the spectrum of viruses known to harbor TF by demonstrating TF antigen and function on Flaviviridae and Coronaviridae. Thus, the ubiquity of TF on viruses as the molecular basis of infectious pathology is supported.

#54

ALEXANDRE AUBERT

PDF · Supervisor: **David Granville**

TITLE

GRANZYME B ORCHESTRATES A DEGRADOMIC AND TRANSCRIPTOMIC LANDSCAPE THAT PROMOTES PRO-INFLAMMATORY AND PRO-FIBROTIC PROGRAMS IN DERMAL FIBROBLASTS

AUTHORS

Alexandre Aubert[1,2,3], Anna Prudova[1,2,3], Jeffrey S. Tang[4,5,6], Jhunam Sidhu[1,2,3], Karen Jung[1,2,3], Richard I. Crawford[2,7] and David J. Granville[1,2,3]

AFFILIATIONS

[1]International Collaboration on Repair Discoveries (ICORD) Centre, Vancouver Coastal Health Research Institute (VCHRI), University of British Columbia (UBC), Vancouver, BC, Canada; [2]Department of Pathology and Laboratory Medicine, University of British Columbia (UBC), Vancouver, BC, Canada; [3]British Columbia Professional Firefighters' Burn and Wound Healing Group, Vancouver Coastal Health Research Institute (VCHRI), Vancouver, BC, Canada; [4]Department of Anesthesiology, Pharmacology & Therapeutics, The University of British Columbia.; [5]Centre for Heart Lung Innovation, Vancouver, BC, Canada; [6]Providence Research, Providence Health Care, Vancouver, BC, Canada; [7]Department of Dermatology and Skin Sciences, University of British Columbia, Vancouver, BC, Canada

ABSTRACT

Background/objectives: Granzyme B (GzmB) is a serine protease with aspase-like activity extensively studied for its perforin-dependent, intracellular role in immune cell-mediated apoptosis. However, in recent years, extracellular GzmB accumulation has been observed in several inflammatory conditions of the skin, including psoriasis, atopic dermatitis, hypertrophic scarring and keloids. In the extracellular milieu, GzmB retains its proteolytic activity and contributes to scarring and fibrosis through the cleavage of specific extracellular matrix (ECM) molecules. Nevertheless, the full repertoire of extracellular GzmB substrates and their impact on pathology remains understudied. Here, we ***hypothesized***that GzmB-mediated cleavage of fibroblast-derived proteins contributes to fibrosis and scarring.

Methodology: To characterize the pathological roles of extracellular GzmB in dermatological conditions, we used a multi omic-approach on primary human dermal fibroblasts treated with GzmB (n=3) or vehicle control (n=3). While conditioned media enriched in GzmB cleavage products were analysed by Terminal Amine Isotopic Labelling of Substrates (TAILS), RNA sequencing was performed on the intracellular fractions. New substrates, as well as signaling pathways up-regulated by GzmB in dermal fibroblasts, were further validated in vitro and in vivo using a system biology approach and disease-relevant human samples.

Results: Results from TAILS revealed that GzmB cleaves numerous structural and non-structural ECM molecules produced by dermal fibroblasts, as well as proteins associated with growth factor binding. GzmB notably cleaves type I collagen derived from fibroblast ECM and from human skin, generating a specific and soluble 35 kDa fragment. GzmB also promotes the release of Transforming Growth Factor (TGF)-b from fibroblast derived ECM, leading to the activation of a TGF-b/Smad signaling pathway in dermal fibroblasts. This observation has been confirmed by RNA sequencing, demonstrating the ability of GzmB to promote a "*TGF-b like*" and an inflammatory transcriptomic response in dermal fibroblasts. Using bioinformatic tools, we demonstrated that GzmB degradomic and transcriptomic signatures were independently converging toward a role for the protease in scarring, fibrosis, and burns. Specific markers of GzmB-dependent TGF-b and pro-inflammatory pathways were further validated at protein levels in skin biopsies from patients suffering from keloids (n=5) and hypertrophic scars (n=5), compared to healthy skin controls (n=5). Finally, we identified that a specific TGF-b-dependent fibrotic marker was reduced in an animal model of thermal injury topically treated with a specific extracellular GzmB inhibitor in comparison to vehicle-treated mice, demonstrating that GzmB can promote TGF-b activation in vivo in burn samples.

Conclusion: GzmB contributes to fibrosis and scarring through multiple mechanisms involving ECM remodeling, inflammation, and TGF-b activation. It consequently represents a promising therapeutic target for the treatment of burns, hypertrophic scars, and keloids.

#55

LANLAN FANG

PDF · Supervisor: **David Huntsman and Yemin Wang**

TITLE

INVESTIGATING THE ROLES OF TRANSFORMING GROWTH FACTOR-BETA AND MITOGEN-ACTIVATED PROTEIN KINASES PATHWAYS IN THE PATHOGENESIS OF DICER1 SYNDROME–ASSOCIATED SARCOMA

AUTHORS

Fang, Lanlan[1]; Zhang, Joyce[1]; Chen, Shary[1]; Dang, Sam[1]; Wang, Shuangyu[2]; Wei, Grace[1]; Choi, Yannes[1]; Senz, Janine[1]; Lynch, Branden J.[1]; Huntsman, David[1,2]; Wang, Yemin[1]

AFFILIATIONS

[1]Department of Pathology and Laboratory Medicine, University of British Columbia, Vancouver, British Columbia, Canada; [2]Department of Obstetrics and Gynaecology, University of British Columbia, Vancouver, British Columbia, Canada

ABSTRACT

Background/objectives: DICER1 syndrome-associated cancers are characterized by hemizygous DICER1 RNase IIIb (*DICER1*^{IIIb}) mutations. Using genetically engineered mouse models (GEMM), we have recently demonstrated that the hemizygous *DICER1*^{IIIb} mutations enable renal sarcoma development from mesenchymal stromal cells (MSCs), which faithfully recapitulate the genetics, histology, and genomics of the human disease. When studying the tumor developmental hierarchy by spatial single-cell transcriptomics analysis, we further found that the TGF-beta pathway activity is repressed along the disease progression, with the lowest activity in differentiated myogenic cells and sarcoma cells, while mitogen-activated protein kinases (MAPK) activity is elevated along tumor progression, with the highest activity in proliferative sarcoma cells. These findings indicate that repression of TGF-beta and activation of MAPK promote *DICER1*^{IIIb} mutation-driven tumorigenesis.

Methods: Mouse cell lines were derived from renal tumors arising from the Dicer1 GEMM mice or the normal kidney. The mutation landscape was determined by whole-exome sequencing. A TaqMan allelic frequency discrimination assay determined mutant Dicer1 transcripts. CRISPR/Cas9-mediated gene knockout was used for gene knockout. Cell growth curves were generated and analyzed using the IncuCyte. The clonogenic assay and scratch assay were performed to assess cell proliferation, colony-forming ability, and cell migration. Gene expression levels were quantified using western blotting and/or RT-qPCR.

Results: Given that SMAD4 is the central mediator of the TGF-beta1 signaling pathway, we knocked out SMAD4 in renal Dicer1 sarcoma cells and found that SMAD4 knockout significantly increased the growth rate and proliferative capacity of the tumor cells. Treatment with TGF-beta1 inhibited tumor cell growth in a dose-dependent manner without affecting normal renal MSCs, decreased migration and colony-forming ability, and downregulated miRNA-processing genes (Dicer1, Drosha, and Dgcr8) and miR-199a-3p and miR-126-3p, the top two abundantly expressed 3p-miRNAs in Dicer1 sarcoma. Furthermore, ERK phosphorylation is elevated in high-grade human DICER1 sarcoma in comparison to low-grade tumors. In addition, regardless of KRAS mutation status, ERK phosphorylation level is higher in multiple Dicer1 sarcoma cell lines than in normal renal MSCs. Lastly, the Dicer1 sarcoma cells were highly sensitive to trametinib treatment, a clinically used MEK2 inhibitor.

Conclusions: Our findings demonstrate that TGF-beta signaling inhibits the proliferation, migration, and colony-forming ability of DICER1 sarcoma cells through suppressing the expression of 3p miRNAs, whose retention is required for tumorigenesis in DICER1 syndrome patients, and DICER1 sarcoma cells are highly sensitive to MAPK inhibition, providing a potential therapeutic approach for further clinical investigation.

#56

DANIELE FERRARI

PDF · Supervisor: **David Granville**

TITLE

EMERGING ROLES OF GRANZYME K IN AGE-ASSOCIATED NEUROINFLAMMATION AND BEHAVIORAL DYSFUNCTION

AUTHORS

Ferrari, Daniele[1,2,3]; Ponomarev, Tatjana[1,2,3]; Zhao, Hongyan[1,2,3]; Granville, David[1,2,3]

AFFILIATIONS

[1] International Collaboration on Repair Discoveries (ICORD) Centre, Vancouver Coastal Health Research Institute, University of British Columbia, Vancouver, BC, Canada.; [2] Department of Pathology and Laboratory Medicine, University of British Columbia, Vancouver, BC, Canada.; [3] British Columbia Professional Firefighters' Burn and Wound Healing Group, Vancouver Coastal Health Research Institute, University of British Columbia, Vancouver, BC, Canada.

ABSTRACT

Background/objectives: Chronic neuroinflammation has emerged as a key contributor to age-related functional decline, resulting from persistent glial activation and the accumulation of pro-inflammatory cytokines. This sustained inflammatory state induces neurotoxicity, accelerating cognitive decline. Granzymes are serine proteases classically known for their cytotoxic roles mediating the elimination of infected or damaged cells. However, emerging evidence indicates that they also exert extracellular, non-cytotoxic inflammatory roles. Notably, Granzyme K (GzmK) levels are elevated in the aging brain and in neurodegenerative conditions, suggesting a role in neuropathologies. This study aims to elucidate the contribution of GzmK to behavioral and neuroinflammatory processes associated with aging.

Methods:

Behavioral phenotypes were assessed in young (≤12 weeks) and aged (70–96 weeks) GzmK knockout (GzmK KO) and wild-type (WT) mice (n = 5–11 per group). Tests included the open field test (locomotion), elevated plus maze (anxiety-like behavior), social recognition test (memory and sociability), and von Frey test (mechanical sensitivity). To model neuroinflammation, young mice received repeated lipopolysaccharide (LPS; 0.25–0.5 mg/ml) injections for 7 days, followed by reassessment using the same behavioral tests. Pro-inflammatory cytokines were quantified post-LPS in the serum. Brain regions including the prefrontal cortex and hippocampus were analyzed for markers of neuroinflammation using immunofluorescence staining for IBA-1 (microglia) and GFAP (astrocytes).

Results: Aged GzmK KO mice exhibited increased locomotor activity, characterized by greater distance traveled and speed, along with reduced freezing behavior in the open field test compared to aged WT controls. GzmK KO mice also exhibited improved social recognition. In young mice, GzmK deficiency reduced mechanical thresholds in the von Frey test, indicative of increased sensitivity, which was further exacerbated following LPS treatment. Notably, young GzmK KO mice did not exhibit LPS-induced increase in anxiety-like behavior and displayed enhanced sociability and social recognition, compared to LPS-treated WT mice. Preliminary analyses revealed increased microglial activation in the prefrontal cortex and hippocampus of WT mice relative to GzmK KO mice. Additionally, WT mice displayed elevated serum TNF-α levels following LPS exposure, suggesting that GzmK deficiency attenuates neuroinflammatory responses.

Conclusions: Our findings identify GzmK as a potential modulator of neuroinflammation and behavior in aging. Targeting GzmK may provide new insights into the mechanisms underlying age-related cognitive and motor decline and offer novel therapeutic opportunities. To further define the molecular mechanisms involved, we will conduct RNA-seq analysis of the hippocampus from aged WT and GzmK KO mice to characterize age-dependent transcriptional changes.

#57

BIANCA RIBEIRO DE SOUZA

PDF · Supervisor: **Philipp Lange**

TITLE

TMATOOLS: POWERING PROCESSING AND INTEGRATION OF TISSUE MICROARRAY (TMA) DATA AT SCALE

AUTHORS

Ribeiro de Souza, Bianca[1,2,3]; Okada Akhlaghi, Hannah[3]; Netto Flores Cruz, Giuliano[4,5]; Lange, Philipp F[1,2]; Anglesio, Michael[3]

AFFILIATIONS

[1]Department of Pathology and Laboratory Medicine, UBC, Vancouver, Canada; [2]Michael Cuccione Childhood Cancer Research Program, BC Children's Hospital Research Institute, Vancouver, Canada; [3]Department of Obstetrics and Gynaecology, UBC, Vancouver, Canada; [4]Department of Statistics, UBC, Vancouver, Canada; [5]Centre for Molecular Medicine and Therapeutics, BC Children's Hospital Research Institute, Vancouver, Canada

ABSTRACT

Background/objectives: Tissue microarrays (TMAs) are a powerful tool in pathology research, enabling high-throughput analysis of hundreds of patient samples simultaneously. However, TMA data processing remains challenged by lack of standardization, often requiring labourious manual steps that are prone to human error. Currently available tools do not provide end-to-end processing of multiple TMAs or do not follow Findable, Accessible, Interoperable and Reusable (FAIR) principles. To address this gap, we aimed to develop *TMAtools*, a FAIR software package designed to integrate, deconvolute, translate, consolidate, and quality-control large-scale TMA datasets with multiple biomarkers and heterogeneous templates.

Methods: *TMAtools* was developed as a user-friendly R package that takes as input one or more TMAs, including TMA map, score sheets, biomarker scoring system, and optional metadata – all as Excel files familiar to pathology workflows. The full pipeline was implemented in a single command to improve accessibility for users without coding experience, while maintaining reproducibility. For each TMA, *TMAtools* employs modular steps to (1) combine all selected biomarker score sheets, (2) deconvolute scores using the TMA map, (3) translate scores using user-specified labels, and (4) consolidate replicate cores into a single representative score per patient. *TMAtools* leverages fully customizable scoring systems that allow both qualitative and numerical scores through an input spreadsheet with translation and consolidation rules. Optionally, datasets with scores from the same patient replicated across different TMAs are reconsolidated, automatically preventing duplication. At each step, *TMAtools* provides intermediate outputs for manual inspection. The final output is a single spreadsheet with the results from all TMAs and the selected biomarker panel, with scores from individual cores, consolidated values, and metadata.

Results: We applied and validated the *TMAtools* pipeline to a multinational cohort study of Endometrioid Ovarian Carcinoma patients (n=1,319) from 32 centres across 6 countries. 19 TMAs were processed for a panel of 17 biomarkers relevant for classification and prognostication of endometriosis-associated ovarian cancers. The final output included results from over 70,000 individual cores with consolidated scores linked to clinical outcomes and other patient metadata. We also employed the *TMAtools*' deconvolution algorithm as an independent module to deconvolute TMAs used for spatial transcriptomic profiling of Neuroblastoma tumours assayed with NanoString's GeoMx. The positions of regions of interest (ROIs) were deconvoluted from the TMA map and linked to respective core and patient IDs needed for downstream analyses.

Conclusions: *TMAtools* is a FAIR tool that enables efficient, reproducible, and traceable processing of TMA data while integrating seamlessly into pathology research workflows. By allowing diverse applications and customization, TMAtools is a valuable resource for biomarker discovery in TMA-based large-scale cancer studies. The R package and tutorials are freely available at edgeresearch-ca.github.io/TMAtools.

#58

GENEVIEVE AMARAL

Resident · Supervisor: **Dr. Christopher Lowe**

NOBLE 84

TITLE

LEVERAGING LOW-COST BLUETOOTH TRACKERS TO OPTIMIZE SPECIMEN LOGISTICS FOR TRANSPLANT PATIENTS: A PILOT ACROSS TWO WESTERN CANADIAN HEALTH AUTHORITIES

AUTHORS

Amaral, Geneviève[1], Tang, Patrick[1,2], Matic, Nancy[1,2], Yuen, Victor T.H.[1,3], Grasa, Katherine[3], Kaufmann, Elisha[3], Lawson, Tanya[2], Young, Matthew[2], Payne, Michael[1,2], Romney, Marc G.[1,2], Stefanovic, Aleksandra[1,2], Musaji, Andrei[1,3], Lowe, Christopher F.[1,2]

AFFILIATIONS

[1]Department of Pathology and Laboratory Medicine, University of British Columbia, Vancouver, BC; [2]Division of Medical Microbiology and Virology, Department of Pathology and Laboratory Medicine, St. Paul's Hospital, Vancouver, BC; [3]Division of Medical Microbiology, Department of Pathology and Laboratory Medicine, Royal Jubilee Hospital and Victoria General Hospital, Victoria, BC

ABSTRACT

Background/objectives:

Viral load (VL) turnaround time (TAT) is a critical determinant of clinical outcomes for solid organ transplant recipients. However, viral load testing is often centralized to reference laboratories. For patients in distant sites, delays in specimen transport are often unmeasured and poorly understood. We evaluated the utility of a low-cost Bluetooth tracking platform to map logistics and identify actionable delay points.

Methods:

We prospectively accessioned Tile Pro trackers (n=20) into the routine cytomegalovirus (CMV) VL workflow between a regional laboratory and centralized virology laboratory over one month. Real-time tracking data was extracted via Python to calculate precise transit intervals across four distinct phases: pre-transport, ground/air transit, central receiving, and final laboratory routing.

Results:

End-to-end mean transport time from regional laboratory accessioning to receipt in the virology lab was 26.6h with 95% arriving within 48h. The transit time was significantly faster for samples transported by air (<8.4h) compared to those transported by ground (16.8h). Although the mean time from arrival at the central lab receiving area to the virology lab was 6.4h, 10% of samples experienced a >22h delay during internal accessioning and routing.

Conclusions:

This study demonstrates that low-cost, consumer-grade Bluetooth technology provides a high-fidelity, scalable alternative to expensive GPS tracking for laboratory quality improvement. By transforming anecdotal delays into objective data, we initiated a collaborative workflow redesign with the accessioning team to enhance the "last-mile" routing of time-sensitive transplant specimens.

#59

EMMA FINLAYSON-TRICK

Resident · Supervisor: **Shaqil Peermohamed**

NOBLE 85

TITLE

ANTIBIOTICS DON'T TAKE WEEKENDS OFF: FEWER BROAD-SPECTRUM DISCONTINUATIONS ON SATURDAYS AND SUNDAYS

AUTHORS

Finlayson-Trick, Emma[1], Shajari, Salomeh[2], Peermohamed, Shaqil[2,3]

AFFILIATIONS

[1]Department of Pathology and Laboratory Medicine, University of British Columbia, Vancouver, BC, Canada; [2]ASPIRES (Antimicrobial Stewardship Programme: Innovation, Research, Education, and Safety), Patient Quality and Safety, Vancouver Coastal Health, Vancouver, BC, Canada; [3]Divisions of Infectious Diseases, Department of Medicine, University of British Columbia, Vancouver, BC, Canada

ABSTRACT

Background/objectives:

Broad-spectrum antibiotic prescribing practices are influenced not only by clinical indication but also by social norms and organizational characteristics. Prior studies have shown less broad-spectrum antibiotic discontinuations occur on weekends compared with weekdays. Whether this pattern exists within Canadian hospitals and our local health system has not been well characterized. This study assessed the impact of the day of the week on broad-spectrum antibiotic initiation and discontinuation in four Canadian hospitals.

Methods:

We conducted a retrospective analysis of pharmacy antimicrobial administration data from December 16, 2023, to January 6, 2025, at four hospitals. Broad-spectrum antibiotics included anti-MRSA (vancomycin, linezolid, daptomycin) and anti-pseudomonal agents (meropenem, imipenem/cilastatin, piperacillin/tazobactam). Prescribing patterns were compared across weekdays, weekends, and statutory holidays. Statistical testing used Kruskal–Wallis and Wilcoxon pairwise tests, as appropriate.

Results:

A total of 9,306 broad-spectrum antibiotic initiations and discontinuations were identified. Antibiotic initiations did not differ by day of the week, or between non-holiday weekdays and weekends/holidays. In contrast, broad-spectrum antibiotic discontinuations varied significantly by day ($p = 0.026$), with fewer discontinuations occurring on Saturdays and Sundays compared with most weekdays ($p < 0.05$). Discontinuations were also significantly lower on weekends/holidays than on non-holiday weekdays ($p < 0.01$).

Conclusions:

While broad-spectrum antibiotic initiation remained consistent throughout the week, broad-spectrum antibiotic discontinuation occurred significantly less often on weekends and holidays, confirming what has been observed in prior studies. This could be due to several factors such as reduced weekend staffing, reduced weekend access to infectious disease specialists and antimicrobial stewardship pharmacists and physicians, and decision fatigue. Future studies can explore the social dynamics that might influence broad-spectrum antibiotic discontinuation and inform targeted antimicrobial stewardship strategies to optimize weekend antimicrobial prescribing practices.

#60

REED HUBER

Resident

NOBLE 86

TITLE

CYTOPLASMIC P16 IMMUNOHISTOCHEMISTRY CORRELATES WITH CDKN2A PATHWAY ALTERATION IN ORAL EPITHELIAL DYSPLASIA AND HEAD AND NECK SQUAMOUS CELL CARCINOMA

AUTHORS

Huber, Reed[1]; Ko, Kevin[1,2]; Hahn, Elan[3]

AFFILIATIONS

[1] Department of Pathology and Laboratory Medicine, University of British Columbia, Vancouver, British Columbia, Canada; [2] Department of Pathology, BC Cancer, Vancouver, British Columbia, Canada; [3] Department of Pathology and Laboratory Medicine, Mount Sinai Hospital, Toronto, Ontario, Canada

ABSTRACT

Background/objectives: A subset of p53 wild-type oral precancerous lesions characterized by disproportionate architectural distortion relative to cytologic atypia remain challenging to diagnose, underscoring the need for a biomarker to aid in their classification. This study is the most comprehensive set of cases to date of abnormal p16 immunohistochemical (IHC) staining with correlation with *CDKN2A* pathway alteration, endorsing that use of p16 IHC is a useful diagnostic and predictive biomarker for a subset of acanthotic precursor and malignant lesions, including carcinoma cuniculatum.

Methods: Here we present 35 cases of unique cytoplasmic p16 IHC staining in oral epithelial dysplasia and head and neck squamous cell carcinoma, and for a subset of cases we correlated the staining patterns with *CDKN2A* mutational status.

Results: Five out of six sequenced cases had a *CDKN2A* mutation and using recently proposed criteria, we recategorized four patients with previously benign diagnoses as p16 abnormal oral epithelial dysplasia.

Conclusions: Careful interpretation of cytoplasmic p16 IHC staining and categorization into recently described p16 abnormal oral epithelial dysplasia helps to capture a subset of patients with challenging acanthotic oral lesions according to genomic etiology, and furthermore can help support the idea that a lesion is progressing along the *CDKN2A* pathway toward carcinoma cuniculatum.

#90

ETHAN KENMUIR

Graduate Student · Supervisor:
Dr. Natalie Prystajecky

T I T L E

INVESTIGATING INFECTIOUS LARYNGOTRACHEITIS VIRUS TRANSMISSION AND VACCINE REVERSION IN BRITISH COLUMBIA USING TARGETED AMPLICON SEQUENCING

A U T H O R S

Kenmuir, Ethan[1,2]; Kuchinski, Kevin[3]; Himsworth, Chelsea[3]; Lin, Gigi[3]; Miller, Jake[2]; Prystajecky, Natalie[1,2]

A F F I L I A T I O N S

[1] Department of Pathology and Laboratory Medicine, University of British Columbia, Vancouver, British Columbia, Canada; [2] Public Health Laboratory, British Columbia Centre for Disease Control, Vancouver, British Columbia, Canada; [3] Animal Health Centre, British Columbia Ministry of Agriculture and Food, Abbotsford, British Columbia, Canada

A B S T R A C T

Background/objectives: Infectious laryngotracheitis virus (ILTV) is a highly contagious upper respiratory disease in chickens. ILTV causes frequent outbreaks in both commercial and backyard poultry flocks worldwide, impacting major poultry-producing regions. In British Columbia (BC), outbreaks are managed through vaccination and biosecurity measures, supported by routine monitoring using diagnostic quantitative polymerase chain reaction (qPCR) and histopathology. However, transmission between farms remains poorly understood, and there is increasing concern that reversion of live attenuated vaccines may contribute to outbreaks. Whole genome sequencing (WGS) is a tool used to investigate viral transmission dynamics; however, the difficult sample matrix and large genome size of ILTV limit its routine application. Partial sequencing, in which informative genomic regions are selectively targeted, presents a potential strategy to overcome WGS challenges. Here, we aimed to develop a targeted sequencing method to better understand the transmission and vaccine reversion of ILTV. We hypothesize that sequencing select regions of the ILTV genome would provide resolution to assess potential vaccine reversion events and infer transmission links among BC poultry farms.

Methods: DNA was extracted from trachea and lung tissues collected from chickens associated with BC ILTV outbreaks (n = 104), along with three ILTV vaccine products administered in BC (AviProLT, LT-Blen, and LT-IVAX). Eight variable regions of the ILTV genome (glycoproteins B, C, G, M, DIE, open reading frame A-B, unique long 0-1, and thymidine kinase) were amplified using a multiplex PCR reaction. PCR products were sequenced on the Oxford MinION Nanopore platform. Phylogenetic trees were assembled from BC sequences, vaccine sequences, and reference sequences obtained from GenBank to visualize genetic relationships among isolates.

Results: Phylogenetic analysis revealed distinct clustering of BC outbreak specimens, largely separate from vaccine and other reference sequences. However, the limited genomic coverage of the partial sequencing approach resulted in large clusters of closely related, indistinguishable, BC strains. Notably, only a small subset of BC ILTV specimens (n = 7) clustered among the vaccine LT-IVAX, suggesting minor influence of vaccine-associated viruses in BC outbreaks.

Conclusions: The partial sequencing method provides an effective sequencing approach for generating informative sequence data to assess potential ILTV vaccine reversion. However, limited genomic coverage and high sequence similarity among BC isolates restrict its utility for fine-scale transmission analysis. Despite this limitation, the scalability of this method supports its use for ILTV surveillance and may help inform vaccination and biosecurity strategies in the BC poultry industry.

KHASHAYAR HANJANI

Resident · Supervisor: **Dr. Kazem Nouri**

NOBLE 87

TITLE

VALIDATION OF CSF KAPPA FREE LIGHT CHAINS ASSAY AS A DIAGNOSTIC BIOMARKER IN MULTIPLE SCLEROSIS

AUTHORS

Hanjani, Khashayar[1], Hall, Kari[2], Cheng, Catherine[1], Nouri, Kazem[1]

AFFILIATIONS

[1] *Department of Pathology and Laboratory Medicine, UBC;* [2] *Provincial Health Services Authority*

ABSTRACT

Background/objectives:

Multiple sclerosis (MS) is a debilitating disease with a complex pathway for diagnosis which involves combining clinical, radiological and biochemical data. Oligoclonal banding (OCB) is the historical biochemical technique that aids in diagnosis of MS. OCB analysis involves examination of paired serum and CSF samples using a gel-based isoelectric focusing technique to separate immunoglobulins based on their isoelectric point. However, OCB is a complex technique that requires batching, significant hands-on time from medical laboratory technologists and qualitative interpretation. These factors increase test turnaround time and require significant human input. Cerebrospinal fluid (CSF) free kappa light chains (FKLC) has recently been added to the McDonald criteria for MS diagnosis as an alternative test to OCB. FKLC in the CSF can be measured on the Optilite analyzer which is the same platform available at Vancouver General Hospital (VGH) for quantifying serum free light chains in lymphoproliferative disorders. This project aims to validate CSF FKLC testing for clinical use and develop an algorithm FKLC and OCB cascade testing that optimizes resource utilization while maintaining diagnostic performance.

Methods:

Performance verification was conducted and included the following components: complex precision, linearity, method comparison, accuracy via spiking study, carryover, and stability.

The study uses samples that have previously had OCB analysis at VGH. Using CSF and serum FKLC values along with CSF and serum albumin levels, FKLC index was calculated for samples.

A case-control approach is being utilized considering OCB results as well as clinical and radiographic criteria for MS diagnosis through chart review.

Receiver operator curve analysis will be conducted to assess the sensitive and specific cutoffs for CSF FKLC level or FKLC index in predicting OCB positivity and MS diagnosis. The Youden Index will be used to identify optimal cutoffs for sensitivity and specificity while diagnostic utility will be further assessed via predictive values and likelihood ratios.

Using this information, an algorithm that combines FKLC analysis with reflex OCB testing when required will be developed.

Results:

The CSF FKLC assay's performance has been verified for clinical use.

Data collection and analysis is ongoing.

Conclusions:

CSF FKLC is an assay that can be used in place of, or in conjunction with, OCB in the MS diagnosis pathway. The performance of this assay on the Optilite platform has been verified for clinical use. Utilizing this assay in British Columbia has the potential to increase efficiency in terms of testing cost, labour, and turnaround time while maintaining or improving overall diagnostic performance.