PATHOLOGY AND LABORATORY MEDICINE

RESEARCH DAY 2022

SCHEDULE & PLATFORM PRESENTATION ABSTRACTS

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Schulich MEDICINE & DENTISTRY

London Health Sciences Centre

Western

MORNING SCHEDULE

9:00 a.m. **Welcome and Opening Remarks**

Dr. David Driman

Chair/Chief, Pathology and Laboratory Medicine,
Schulich Medicine & Dentistry, Western University

9:15 a.m. **Keynote Address**

Dr. Michael J. Strong

President, Canadian Institutes of Health Research
Distinguished University Professor,
Neurology and Pathology and Laboratory Medicine
Schulich Medicine & Dentistry, Western University

10:15 a.m. Break

10:30 a.m. **Platform Presentations 1**

Lindsay Ninivirta

Hao Li

Jonathan Keow

11:15 a.m. Break

11:30 a.m. **Platform Presentations 2**

Kathleen Rooney

Lara Gerhardt

Peter Zeng

12:15 p.m. Lunch Break

AFTERNOON SCHEDULE

1:30 p.m. **Poster Presentations 1**

Concurrent session 1A:
Cardiovascular, Respiratory Health and Metabolic Diseases

Concurrent session 1B:
Epigenetics

Concurrent session 1C:
Infection, Immunity, and Inflammation

Concurrent session 1D:
Interdisciplinary Research in Health and Education

2:45 p.m. **Poster Presentations 2**

Concurrent session 2A:
Test Utilization, Optimization and Quality Assurance

Concurrent session 2B:
One Health

Concurrent session 2C:
Oral Biology and Medicine

Concurrent session 2D:
Cancer Biology

4:00 p.m. **Platform Presentations 3**

Concurrent session 3A:
Bioinformatics and Data Science

Concurrent session 3B:
Digital Pathology

Concurrent session 3C:
Regenerative and Transplantation Medicine

Concurrent session 3D:
Pathogenesis of Neurologic Diseases

KEYNOTE

“Advancing our understanding of neurodegeneration. Is there a need for objectives?”

Biography

Dr. Michael J. Strong was appointed President of the Canadian Institutes of Health Research effective October 1, 2018. Prior to joining CIHR, Dr. Strong was Dean of the Schulich School of Medicine and Dentistry and a Distinguished University Professor at Western University. From 2000 to 2010, he served as Chief of Neurology and Co-Chair of the Department of Clinical Neurological Sciences at the London Health Sciences Centre and Western University. He also served as Co-Chair of the Canadian ALS Research Consortium and is a former member of the Board of Directors of the ALS Society of Canada.

Dr. Strong’s clinical research has focused on understanding the cellular biology of amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig’s disease. He is particularly interested in the occurrence of non-motor manifestations of the disease including the cognitive, behavioural, and emotional syndromes associated with ALS. This work has led to the development of international consensus criteria for the diagnosis of the syndromes of frontotemporal dysfunction in ALS. In the research laboratory, his work has included developing an understanding of the pathological cellular inclusions in degenerating neurons in ALS, including the roles of altered RNA and tau protein metabolism.

Dr. Strong has published over 200 peer-reviewed articles and 29 chapters, edited four textbooks and given over 175 lectures on ALS throughout Canada and around the world. He is the recipient of both the Sheila Essey Award and the Forbes Norris Award, the only Canadian to have received both awards for ALS research. He was also awarded the Queen Elizabeth II Diamond Jubilee Medal in 2012 for his contributions to ALS research and care, and is a Fellow of the Canadian Academy of Health Sciences.

Dr. Strong earned his degree in medicine at Queens University in Kingston, undertook neurology training at Western University, and completed postgraduate studies at the Laboratory of Central Nervous System Studies (Director – D. Carleton Gadjusek, Nobel Laureate) at the National Institutes of Health, Bethesda, Maryland.

to see more, please visit: https://cihr-irsc.gc.ca/e/10308.html

ORAL PRESENTATIONS

Time	First Name	Last Name	Title
10:30 a.m.	Lindsay	Ninivirta	The Effects of the COVID-19 Pandemic on Breast Cancer Positivity Rates
10:45 a.m.	Hao	Li	Assessment Variability in Medical Education: Why Does it Happen?
11:00 a.m.	Jonathan	Keow	Validation and application of a BRAF V600E antibody to a variety of clinical settings
11:30 a.m.	Kathleen	Rooney	Identification of a Unique Diagnostic Episignature in 1p36 Deletion Syndrome
11:45 a.m.	Lara	Gerhardt	Investigating IL-12 family cytokine involvement in modulating CD39 expression by CD8+ T-cells using an immunogenic neuroblastoma model
12:00 p.m.	Peter	Zeng	A Clinically Translatable Immune-based Classification of HPV-associated Head and Neck Cancer with Implications for Biomarker-Driven Treatment Deintensification and Immunotherapy

ORAL PRESENTATION 1

Presenter's Name: Ninivirta, Lindsay

Additional Author(s): Tran C, Driman DK

Abstract Title: The Effects of the COVID-19 Pandemic on Breast Cancer Positivity Rates

Abstract:

Introduction: The COVID-19 pandemic has created unprecedented challenges in healthcare service delivery and patient access to healthcare services. In Ontario, a province-wide ramping down of non-emergent activities between March and June 2020 resulted in significantly reduced surgeries and screening tests due to public health mandates. The aim of this study is to determine whether health care changes as a result of COVID-19 have had an impact on breast biopsy patterns as measured by case volume and positivity rates.

Methods: A retrospective cohort analysis was performed; breast biopsy cases were identified through a search of the departmental pathology database. All breast biopsies collected from March 15, 2018 to March 15, 2021 were included in the study. We used the index date of March 15, 2020 for the COVID-19 cohort as this date represented the start of the province-wide ramping down of healthcare services. Cases were grouped based on whether they were diagnosed before or after the index date. The diagnoses were then slotted into the following categories: invasive mammary carcinoma, ductal carcinoma in situ (DCIS) and lobular carcinoma in situ (LCIS), atypia, and benign. Statistical analysis was performed to compare biopsy volume rates and positivity rates before and after the index date by subdividing cases into pre-COVID-19 and COVID-19 cohorts.

Results: Our results show no significant difference in median age between the pre-COVID-19 cohort and COVID-19 cohort (age 57.5 years, IQR 20.5 years and age 57 years, IQR 22 years respectively). There was a higher biopsy rate per month in the pre-COVID-19 group compared to the COVID-19 group (133 cases per month, versus 121 cases per month). There was no significant difference across the diagnostic categories in the pre-COVID-19 and COVID-19 cohorts for rates of invasive mammary carcinoma (31.4% versus 29.9%), rates of DCIS/LCIS (6.4% versus 6.7%), atypia (5.2% versus 5.8%) and benign samples (57.0 % versus 57.7%).

Discussion: These findings show that during the first year of the COVID-19 pandemic, biopsy volume rates were reduced compared to pre-COVID rates. However, invasive mammary carcinoma rates were not significantly different in the COVID-19 group compared to the pre-COVID-19 group. This finding is significant in that it has the potential to guide resource allocation and determine where resources may need to be directed to optimize patient outcomes.

ORAL PRESENTATION 2

Presenter's Name: Li, Hao

Additional Author(s): Aziz SJ, Ninivirta L, Driman DK, Watling CJ, Goebel E

Abstract Title: Assessment Variability in Medical Education: Why Does it Happen?

Abstract:

Introduction: Assessment variability in medical education is a phenomenon whereby multiple assessors observing a trainee performing the same task evaluate the trainee differently. A major contributor is uncertainty regarding assessment criteria. Previous interventions to provide clearly-defined criteria, in formative evaluations, have not always resulted in assessment consistency. We aim to find reasons behind this by exploring how assessment criteria affect the cognitive processes of evaluators. This is particularly relevant with the advent of increased assessments in Competency Based Medical Education (CBME) centered Pathology training programs.

Methods: We used descriptions of CBME Entrustable Professional Activities (EPAs) as a model for well-stipulated evaluation criteria. Pathologists, blinded to the true objectives, participated in a 2-part interview. In part 1, they were shown the EPA titles only, and in part 2, the full descriptions. In both parts, participants elaborated on their perceived expectations that each EPA held for a pathology resident. They were finally asked to reflect on how the descriptions affected their thinking around each EPA. The interviews were recorded, transcribed, and subjected to thematic analysis.

Results: Eight Pathologists participated in the study and expressed differing responses to the criteria. For some items, there was disagreement on whether the criteria were valid, due to contrasts with the faculty's own experience as a trainee and with daily clinical work. Certain items were seen as intrinsically "nebulous" with the descriptions adding more confusion. Some participants noted that the criterion descriptions themselves contained internal inconsistencies that were challenging to interpret. Participants also admitted to not necessarily reading the criteria in depth. As a result of all this, faculty described varying approaches to how they might assess a resident even when reading the same criteria.

Discussion: Even with stipulated assessment criteria in medical education, assessment variability may be perpetuated. Factors may be intrinsic to the evaluation items and descriptions themselves, or be extrinsic in the assessor's attitudes towards the criteria. Therefore, interventions to mitigate assessment variability which focus only on criterion clarity and consistency training may be ineffective, as they do not address the feelings and biases that assessors themselves bring to the evaluation process.

ORAL PRESENTATION 3

Presenter's Name: Keow, Jonathan

Additional Author(s): Mura M, Wehrli BM

Abstract Title: Validation and application of a BRAF V600E antibody to a variety of clinical settings

Abstract:

Introduction: BRAF is a proto-oncogene involved in MAPK/ERK signal transduction pathway and mutations in this gene are associated with oncogenesis. The most common activating mutation is a V600E point mutation but its identification is limited to Next Generation DNA sequencing (NGS), a technique with a relatively long turnaround time. However, this information has a significant diagnostic and prognostic implication. Here we validate an immunohistochemical test with a quick turnaround time that is sensitive and specific to the BRAF V600E mutation.

Methods: Eighty tissue samples between 2018 and 2021 were identified from patients with advanced melanoma, colon adenocarcinoma and Hairy Cell Leukemia. Next generation sequencing was previously performed on the same tissue or concurrent aspirated material in all cases. These included 31 skin or lymph node resections for melanoma (12 cases with BRAF V600E mutation, 19 without), 38 colon resections for adenocarcinoma (13 with BRAF V600E mutation, 25 without), 11 bone marrow aspirates and trephine biopsies for Hairy Cell Leukemia (8 with BRAF V600E mutation, 3 without). BRAF V600E immunohistochemistry (VE1, Abcam, 1:100) was performed on tissue sections from each case on a Dako OMNIS platform (Agilent, Santa Clara). VE1 stained slides were reviewed by a pathologist, and scored according to cytoplasmic staining intensity.

Results: There was strong staining in 10 of 12 melanoma cases with V600E mutation and 2 were indeterminate. No staining in all 19 melanoma cases without BRAF V600E mutation. There was strong staining in 10 of 13 colon adenocarcinoma cases with V600E mutation and 3 had weak staining. No staining in 16 of 25 cases without BRAF V600E mutation, and 8 were indeterminate. One case without a BRAF V600E mutation had weak staining, equivocal to the weakly positive cases. There was strong staining in 7 of 8 bone marrow cases with V600E mutation and 1 was indeterminate. No staining in all 3 cases without BRAF V600E mutation.

Discussion: These data illustrate sensitivity of 83-100% for melanoma, 77-100% for colon cancer and 88% for Hairy Cell Leukemia, and specificity of 100% for melanoma, 64-96% for colon cancer and 100% for Hairy Cell Leukemia. Further work is required to optimize staining for colonic tissue. However, we demonstrate a viable assay for expediting Lynch Syndrome screening in colon cancer cases and provide enhanced diagnostic clarity for cases of suspected Hairy Cell Leukemia.

ORAL PRESENTATION 4

Presenter's Name: Rooney, Kathleen

Additional Author(s): Kerkhof J, McConkey H, Levy MA, Relator R, Sadikovic B

Abstract Title: Identification of a Unique Diagnostic Episignature in 1p36 Deletion Syndrome

Abstract:

Introduction: The 1p36 deletion syndrome (1p36DS) is the most common terminal deletion syndrome in humans, occurring in approximately 1 in 5000 births. Prevalent clinical features include hypotonia, severe developmental delay, growth abnormalities, craniofacial dysmorphism, cardiomyopathy and seizures. 1p36DS is considered a contiguous gene disorder, with the mechanisms of disease and genes involved not well characterized. An expanding number of neurodevelopmental disorders (NDDs), associated with genetic alterations, have demonstrated distinct changes in the DNA methylation profile. These epigenetic changes, called episignatures, are highly consistent and specific amongst individuals affected by the same disorder. In this study we assess DNA methylation profiles of individuals with confirmed 1p36 deletions and identify novel insights into the molecular mechanisms of the disorder.

Methods: We performed analysis of genome-wide DNA methylation of peripheral blood from a cohort of 19 patients with 1p36DS using the Illumina 850K BeadChip array. We applied our established bioinformatic discovery pipeline to compare the cohort against a subset of age and sex matched controls from our EpiSign Knowledge Database. Methylation levels for each CpG probe were measured and 100 differentially methylated probes were used for signature discovery. The robustness and sensitivity of the selected probes were tested using Euclidean hierarchical clustering and multidimensional scaling as well as multiple rounds of leave-4-out cross validation. A support vector machine classifier was constructed to confirm the specificity of the episignature and its ability to classify the disorder appropriately and distinctly from other defined episignatures in other NDDs with overlapping clinical presentation.

Results: Our results demonstrate the evidence of a unique and highly specific episignature in patients with 1p36DS. A critical region of the deletion was identified, shared by all patients with the common aberrant DNA methylation pattern. The sensitivity and specificity of this signature was further confirmed by comparing it to over 1000 patients with other NDDs.

Discussion: These findings provide a better understanding of the molecular mechanisms of 1p36DS by highlighting regions of differential methylation across the genome as well as a critical deletion region, where candidate genes may exist. This highly specific episignature can be used for molecular diagnosis of 1p36DS.

ORAL PRESENTATION 5

Presenter's Name: Gerhardt, Lara

Additional Author(s): Figueredo R, Maleki Vareki S

Abstract Title: Investigating IL-12 family cytokine involvement in modulating CD39 expression by CD8+ T-cells using an immunogenic neuroblastoma model

Abstract:

Tumour-reactive CD8+ T-cells play a critical role in tumour control. Several studies demonstrate that tumour-reactive CD8+ tumour infiltrating lymphocytes (TILs) can be defined by the expression of CD39. CD39 is commonly considered an immunosuppressive enzyme, as it depletes ATP. However, CD39 is also implicated in processes such as mitigating activation induced cell death, mediating lymphocyte trafficking and cell-cell interactions, which are important for tumour-reactive CD8+ TIL function. It is unclear whether CD39 expression is modulated by putative anti-tumour factors or tumour-intrinsic mechanisms. The phenotype and anti-tumour response of CD8+ TILs can be modulated by cytokine signalling. IL-12 and IL-27 have established roles in promoting effector T-cell differentiation, expansion, and cytotoxic activity. Both cytokines are implicated in the upregulation of CD39 by T regulatory cells, suggesting it may regulate CD39 expression in other cells including tumour-reactive CD8+ T-cells. We hypothesize that IL-12 and IL-27 induce CD39 upregulation on CD8+ T-cells, resulting in improved anti-tumour immunity.

To address the first part of our hypothesis, we used a syngeneic neuroblastoma mouse model. CD8+ T-cells isolated from naïve or neuro-2a (neuroblastoma) primed mice were stimulated in vitro ± IL-12 or IL-27. Flow cytometry was used to determine the phenotype of CD8+ T-cells. We found CD8+ T-cells stimulated with IL-12 or IL-27 had higher expression of CD39 compared to stimulated controls. Next, we inhibited IL-12 activity in vivo, to study the effect on CD8+ TIL phenotypes and anti-tumour activity. Mice with neutralized IL-12 activity showed reduced tumour-specific CD39+CD8+ TIL frequency compared to isotype control treated mice. Together, these results establish that IL-12 and IL-27 are associated with CD39 induction on CD8+ T-cells in vitro and in vivo. Future experiments will assess the functionality of CD39+CD8+ T-cells using ex vivo cytotoxicity assays. Data generated in this study will provide novel information of the mechanism of CD39 induction and its effect on CD8+ T cell function, which can be exploited to improve future cancer therapies.

ORAL PRESENTATION 6

Presenter's Name: Zeng, Peter

Additional Author(s): Cecchini MJ, Barrett J, Shammas-Toma M, De Cecco L, Serafini M, Cavalieri S, Licitra L, Hoebers F, Brakenhoff R, Leemans C, Scheckenbach K, Poli T, Wang X, Liu X, Laxague F, Prisman E, Poh C, Bose P, Dort J, Shaikh M, Ryan S, Dawson A, Khan M, Howlett C, Stecho W, Plantinga P, da Silva S, Hier M, Khan H, MacNeil D, Mendez A, Yoo J, Fung K, Lang P, Winquist E, Palma D, Ziai H, Li S, Boutros P, Mymryk J, Nichols AC

Abstract Title: A Clinically Translatable Immune-based Classification of HPV-associated Head and Neck Cancer with Implications for Biomarker-Driven Treatment Deintensification and Immunotherapy

Abstract:

Introduction: Human papillomavirus-associated (HPV+) head and neck squamous cell carcinoma (HNSCC) is the fastest rising cancer in North America. There is significant interest in treatment de-escalation for these patients given the generally favourable prognosis. However, 15-30% of patients recur after primary treatment, reflecting a need for improved risk-stratification tools. We sought to develop a molecular test to predict the survival of patients with newly diagnosed HPV+ HNSCC.

Methods: We created a prognostic score (UWO3) that was successfully validated in six independent cohorts comprising 906 patients, including blinded retrospective and prospective external validations. Transcriptomic data from two aggressive radiation de-escalation cohorts were used to assess the ability of UWO3 to identify patients who recur. Multivariate Cox models were used to assess the associations between the UWO3 immune class and outcomes.

Results: A three-gene immune score classified patients into three immune classes (immune rich, mixed, or immune desert) and was strongly associated with disease-free survival in six datasets, including large retrospective and prospective datasets. Pooled analysis demonstrated that the immune rich group had superior disease-free survival at 5 years to the immune desert (HR= 9.0, 95% CI 3.2–25.5, P=3.6x10-5) and mixed (HR=6.4, 95%CI 2.2–18.7, P=0.006) groups after adjusting for age, sex, smoking status, and AJCC8 clinical stage. Finally, UWO3 was able to identify patients from two treatment de-escalation cohorts who remain disease-free after aggressive de-escalation to 30 Gy radiation.

Discussions: The UWO3 immune score could enable biomarker-driven clinical decision-making for patients with HPV+ HNSCC based on robust outcome prediction across six independent cohorts. The superior survival of immune rich patients supports de-intensification strategies, while the inferior outcomes of the immune desert patients suggest the potential for intensification and/or immunotherapy. Prospective de-escalation and intensification clinical trials are currently being planned.

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