UNIVERSITY OF SASKATCHEWAN

University of Saskatchewan

Department of Medicine

Research Day

May 5, 2023

Program and Abstracts

PROGRAM

10:00-10:05
Opening comments
Lawson J

10:05-10:30
<u>Keynote address</u>: Alyson Kelvin, PhD
Scientist at the Vaccine and Infectious Disease Organization (VIDO)
Title: The acute and continuing impacts of emerging viruses

<u>Faculty Session</u>

10:30-10:42
High pandemic related mortality amongst people with HIV in Saskatchewan, Canada
Wong A, Hall K, Craddock S, Trecker M, Lang R, Myrah D, Karunakaran K, Medu L

10:43-10:55
Reasons for withholding tissue Plasminogen Activator (tPA) administration during the COVID-19 pandemic at a tertiary stroke centre
Pourhaj M, Whelan KR, Graham B

10:56-11:08
Induction of Th2 cell tolerance and CD4+CD40L+CD25+CD127- regulatory T cells by human regulatory dendritic cells from allergic donors
Ness S, Messing M, Rudulier CR, McNagny K, Gordon JR

11:09-11:21
Incidence of primary renal disease in the adult Saskatchewan population from 2002-2018
Prasad B, Sharma A, Garg A, Dokouhaki P

11:22-11:34
māmawōhkamātowin (working together) to enhance wellness
Kirychuk S, Rabbitskin N, Bighead S, Karunanayake C, Thompson B, Longjohn C, Davis B, Ermine P, Dolovich L, Dosman JA, Fenton M, Graham H, Lamarche L, Jacobson N, Turner T, Ramsden VR

11:35-11:47
Preliminary analysis of the association between time since pain onset and shoulder kinematics in people with rotator cuff disorders
Lang AE

11:48-12:00

Improving the quality of POCUS use by IM residents – Focus on image archiving

Kolbenson L, Oro A

12:01-12:13

Blood and hand surface lead in veterinary workers using lead shielding during diagnostic radiography

Mayer M, Feng T, Sukut S, Wiebe S, Parker S, Blakely B, Koehncke N

12:14-12:26

Novel small molecule therapies that inhibit neurodegeneration fill a major therapeutic gap in the treatment of MS

Levin MC, Salapa HE, Thibault PA, Libner CD, Ding Y, Clarke JPWE, Kalyaanamoorthy S, Ganesan A, Hutchinson C, Hammond SA, Vizeacoumar FS, Alcorn J, Page B

12:26-12:30

Closing comments

Lawson J

12:30-13:00

Lunch and conversation

Location


Health Sciences Building 1B21 Lounge
B-WING | FIRST FLOOR
1B21 Lounge
Open to GD50 Below
1B23
1B29
1B35
1B37 Meeting Room
B124
B128 Common Equipment Core Facility
B133
B109D
B109C
B109A Student Lab
B106
B104 Student Lab
B109B Histology Core Facility
Open to GD07 Below
1B06 Meeting Room
1B05 Meeting Room
1B03 Classroom
1B01
Lockers
1C01 Student Lounge
1B11 Classroom
To RUH
1A60 Classroom
Link to RUH
1A04 Meeting Room
1A03 Meeting Room
1A10.2 Meeting Room
Lockers
1A10 Office Suite
To Health Sciences E-Wing
1A50
1A30
1A20
Link to E-Wing
Dentistry
Entrance
Directory
First Floor
1A03 Meeting Room
1A04 Meeting Room
1A10.2 Meeting Room
1A60 Classroom
1B05 Meeting Room
1B06 Meeting Room
1B37 Meeting Room
1B03 Classroom
B104 Student Lab
B109A Student Lab
1B11 Classroom
1B21 Lounge
1C01 Student Lounge
Elevator
Meeting Rooms
'A' Wing
'B' Wing
'C' Wing
'D' Wing
D-Wing
B-Wing
C-Wing
A-Wing
Dentistry
E-Wing
N
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Health Sciences
HEALTHSCIENCES.USASK.CA

ABSTRACTS

HIGH PANDEMIC-RELATED MORTALITY AMONGST PEOPLE WITH HIV IN SASKATCHEWAN, CANADA

Wong A, Hall K, Craddock S, Trecker M, Lang R, Myrah D, Karunakaran K, Medu L

Saskatchewan, a Canadian Prairie province, faces a complicated HIV epidemic characterized by high rates of transmission due to injection drug use (IDU) and disproportionate representation of younger persons, women, and persons of Indigenous ethnicity. HIV incidence in Saskatchewan in 2021 was 19.7 per 100,000, 4.5 times higher than the Canadian average. Concurrently, during the COVID-19 pandemic, the recreational use of synthetic opioids such as fentanyl increased, leading to high numbers of overdose events & deaths. We characterized the difference in cascade of care outcomes & mortality amongst people with HIV (PWH) living in southern Saskatchewan during the COVID-19 pandemic.

We conducted a retrospective cohort study for all PWH cared for in the Infectious Diseases Clinic (IDC) at Regina General Hospital between December 31/19 and June 10/22. Age, sex, ethnicity & primary mode of HIV acquisition were collected from the IDC database, along with cascade of care & mortality data. Deaths, including most likely cause of death were characterized via individualized case review.

On December 31/19, IDC cared for 518 PWH. This increased to 585 by June 10/22. Amongst the current cohort, 245 (42%) were female, 163 (28%) were ≤35 years old, 306 (52%) were Indigenous, and 318 (54%) had acquired HIV through IDU. Cascade of care indicators worsened during the COVID-19 pandemic. 58.1% of the cohort were retained in care & 76.1% virally suppressed (HIV RNA ≤ 200 copies/mL) in December 2019, decreasing to 51.3% retained (p=0.02) & 68.8% suppressed (p=0.06) by June 2022.

There were 80 deaths during the study period, representing 15.4% of the cohort from the end of 2019. Most deaths (49, 61.3%) were due to suspected or confirmed drug overdose. 10 (12.5%) additional deaths occurred due to complications from IDU (i.e., sepsis). No deaths were directly attributable to COVID-19. Most who died had acquired HIV from IDU (69/80, 86%).

We describe intersecting epidemics of HIV and IDU disproportionately affecting high-risk populations, leading to significant morbidity & mortality during the COVID-19 pandemic. Contributing factors may have included disruption of safe opioid supply and disrupted access to harm reduction services due to COVID-19. Comprehensive population-level harm reduction and addictions management strategies are urgently needed to reduce morbidity & mortality from drug use amongst PWH in Saskatchewan.

Reasons for withholding tissue Plasminogen Activator (tPA) administration during the COVID-19 pandemic at a tertiary stroke centre.

Pourhaj M, Whelan KR, Graham B

Stroke is a leading cause of death and disability worldwide, including Canada. Treatments for stroke are time dependent and IV tPA for acute ischemic stroke decreases the chance of disability at 90 days if given within 4.5 hours of symptom onset. The onset of the Covid-19 pandemic was initially associated with a decrease in acute stroke treatment with thrombolysis across North America. These decreases seemed transient, with a rebound in numbers seen in other provinces across Canada as widespread lockdown orders were lifted. However, a rebound in thrombolysis was not seen at Royal University Hospital (RUH) in Saskatoon, Saskatchewan during the same period. We will analyze documented reasons why thrombolysis was withheld.

We conducted a retrospective chart review of adult patients with ischemic strokes presenting within 4.5 hours of symptom onset to the RUH from March 2019 –January 2021. We received a waiver of consent from the Research Ethics Board.

128 patients met the inclusion criteria. Statistical analysis is ongoing.

Initial results suggest that there are similar reasons for withholding tPA before and after the Covid-19 pandemic. The main reasons include rapidly resolving/resolved symptoms and a documented tPA exclusion criterion.

Induction of Th2 cell tolerance and $CD4^+CD40L^+CD25^+CD127^-$ regulatory T cells by human regulatory dendritic cells from allergic donors

Ness S, Messing M, Rudulier CR, McNagny K, Gordon JR

In asthmatic individuals, otherwise innocuous stimuli (e.g., pollen) induce inflammatory Th2 responses in place of the regulatory T cell (Treg) responses seen in healthy individuals. Several agents (e.g., IL-10) have been identified with the ability to skew differentiating dendritic cells (DC) towards regulatory phenotypes (DCreg), which then induce Treg responses among human Th2 cells and in murine models. In the presence of cyclosporine (DC-CsA), vasoactive intestinal peptide+IL-10 (DC-VIP/10), or stimulatory agonists (DCstim), we generated dendritic cells from monocytes and loaded them with specific allergen(s). We characterized our induced DCreg/DCstim via ELISA and, through collaborative efforts, by means of CyToF and RNA sequencing. We also examined their abilities to suppress autologous *ex vivo* Th2 responses in mono- or dual allergen-sensitive allergic donors, and their ability to convert Th2 cells into functionally regulatory Treg marker-positive cells. Both DCreg expressed lower levels of HLA-DR, CD40 and CD86 than DCstim, but they also expressed DC-SIGN, ILT2, ILT3 and CCR4, as well as higher levels of IL-10 and TGFβ and higher IL-10:IL-12 expression ratios. CyToF and RNAseq analysis demonstrated distinct characteristics that were unique to each DC population. Both DCreg effectively suppressed allergen-specific Th2 proliferation and Th2-type cytokine expression (e.g., IL-5, IL-13; 84-99% reductions) by cells that were exposed to allergen-pulsed DCstim; furthermore, they induced CD40L+CD25+CD127- Treg, which in turn could effectively suppress activation of down-stream allergen-specific Th2 cell responses. We have shown that our DCreg are able to generate functionally suppressive CD40L+CD25+CD127- Treg. Our collaborative protocol involving CyToF and RNA sequencing techniques resulted in an in-depth phenotypic characterization of our novel (DC-CsA) and more established (DC-VIP/10) in-house DCreg, which sheds light on the possible mechanism(s) of action for these DCreg and contributes to the goal of identifying and standardizing the ideal DCreg candidate for clinical use in the context of allergy.

Incidence of Primary Renal Disease in the Adult Saskatchewan Population from 2002-2018

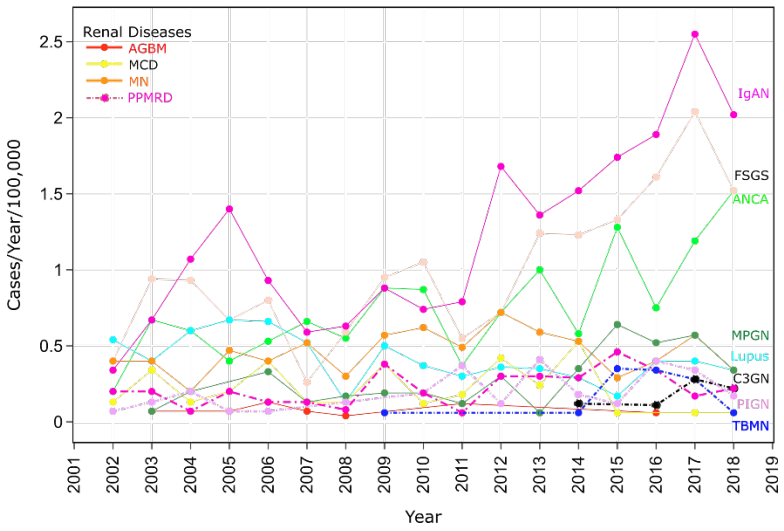
Prasad B, Sharma A, Garg A, Dokouhaki P

The incidence of end stage kidney disease (ESKD) for Saskatchewan (SK) varies from 16.3 to 18.6/100,000 (2011 to 2020). Glomerulonephritis (GN) is the third most common cause of ESKD in patients initiating dialysis or receiving a kidney transplant in Canada. So far, no studies have examined the incidence and prevalence of GN in SK and its relative contribution to ESKD. We decided to investigate the relative frequencies of GN in SK based on sex and age, rural vs urban, access to care and relationship to geographical hotspots (mines and refineries).

A retrospective study was conducted over a period of 17 years from January 2002-December 2018 on all the adult renal biopsies (n = 3509) done at Royal University Hospital, Saskatoon, Saskatchewan, Canada. The patients with renal diagnoses most consistent with primary glomerulopathy were selected (n= 1372). Demographic (postal codes, age, gender), laboratory parameters (serum creatinine, eGFR, serum albumin, UACR, 24hr urine protein), and details of renal biopsy (diagnosis, date of biopsy) were collected and analyzed. ArcGIS software was used for geolocation analysis.

The GN Incidence over the study period overall rose from 4.6 in 2002 to 13.4 in 2018 per 100,000 per year (3.5-fold increase). The median age of the study subjects was 50 years, with 40% in the 18-44 years range. 58% of the cases were male. IgA nephropathy was the most frequently identified in biopsy (25.5 % cases) across the province over the study period. 64% of the total GN cases resided in the cities, with 3/4th of the cases based in Regina and Saskatoon.

The present study concludes that the incidence of GN increased between 2002 and 2018, with substantial variability in the incidence of individual glomerular diseases. Significant geographic clustering of glomerular diseases was seen in Regina and Saskatoon.



Incidence (Cases Per Year Per 100,000)

Year	2002	2018	Total Incidence
IgAN	0.34	2.02	2.54
ANCA	0.2	1.52	2.05
FSGS	0.4	1.52	1.56
Lupus	0.54	0.34	0.9
MN	0.4	0.34	0.82
MPGN	0	0.34	0.5
C3GN	0	0.22	0.45
PPMRD	0.2	0.22	0.4
PIGN	0.07	0.17	0.36
MCD	0.13	0.06	0.14
TBMN	0	0.06	0.09
AGBM	0	0	0.06

Figure 1: Incidence of GN in Saskatchewan during the period 2002-2018.

māmawōhkamātowin (working together) to enhance wellness

Kirychuk S, Rabbitskin N, Bighead S, Karunanayake C, Thompson B, Longjohn C, Davis B, Ermine P, Dolovich L, Dosman JA, Fenton M, Graham H, Lamarche L, Jacobson N, Turner T, Ramsden VR

Context: When environmental tobacco smoke (ETS) is combined with other home-based exposures such as mold the risks to respiratory health are dramatically increased. **Objective:** To understand the relationships between the house, ETS and respiratory health outcomes of those living in the house. **Design:** The overall design was informed by the integration of community-based participatory research and transformative action research. This approach facilitated the process of co-creation, identifying issues of concern to the community, and utilizing the strengths and contributions of the community. **Setting and Participants: O**ne adult from each of the 238 homes in Sturgeon Lake First Nation, Saskatchewan, Canada. **Intervention(s):** Co-created community-based survey and house assessments. **Results:** The participation rate was 100% with 238 of 238 houses participating in both the survey and the house assessment. Almost half (47%) of the houses were smoke-free; and crowding was present in 67% of the houses with 19% having more than two persons/bedroom. House assessments revealed: 58% of homes had visible mold; 39% had a moldy/musty/mildew smell in the house with 65% of with the smell always present; and 74% reported dampness in the house. Residents in the houses were treated for: wheeze (34.3%); bronchitis (27.9%); ear infection (23%); asthma (19.6%); tonsillitis (15.7%); pneumonia (13.2%); croup (9.4%); and respiratory viruses (8.0%). In the last five years hospitalizations for respiratory conditions were: pneumonia (14.8%); bronchitis (11.9%); asthma (9.4%); ear infection (8.0%); and tonsillitis (4.8%). When crowding was present in the house, the home was more frequently smoke-free. Moldy smell and visible mold in the house were significantly associated with respiratory health effects including tonsillitis, bronchitis, pneumonia, respiratory viruses, asthma, croup, ear infections, and wheeze. Having a moldy smell was strongly associated with both treatment and hospitalization for these conditions. **Conclusions:** Although smoke-free homes were important; mold in homes was more strongly associated with both treatment and hospitalization for respiratory conditions.

Preliminary analysis of the association between time since pain onset and shoulder kinematics in people with rotator cuff disorders

Lang AE

Upper limb pain is extremely common. The most frequent cause of pain and disability of the upper limb is injury to the rotator cuff muscles. Harmful movement strategies may be related to the progression of rotator cuff disorder. The purpose of this abstract was to test the association of time since pain onset and shoulder kinematics from a preliminary rotator cuff disorder dataset. It is hypothesized that longer time since pain onset will be associated with more harmful movement patterns (increased humeral internal rotation, increased scapular internal rotation, decreased scapular upward rotation). Seventeen individuals with chronic rotator cuff-related pain were assessed. Upper limb motion was measured during work-related activities and functional daily life tasks. Thoracohumeral (elevation and axial rotation) and scapular (internal rotation, upward rotation, tilt) angles were calculated for each task, and the change in angle was extracted. Pearson correlation coefficients ($p < .05$) quantified the relationship between each outcome and time since pain onset, in years. In this preliminary dataset, time since pain onset was associated with humeral elevation ($r = -.58$, $p = .01$) and humeral axial in the Overhead Reach ($r = .-.51$, $p = .03$). Trends suggest scapular upward rotation in the Overhead Reach ($r = -.42$, $p = .08$) and scapular internal rotation in the Comb Hair ($r = .31$, $p = .21$) and Overhead Reach ($r = .35$, $p=.14$) relationships may reach significance with the full dataset. Longer time since pain onset resulted in decreased humeral internal rotation during the Overhead Reach, and possibly increased scapula internal rotation and scapular upward rotation, partially aligning with our hypotheses. Reduced humeral elevation with time since pain onset may be a protective mechanism in response to other alterations. Final conclusions will be made upon completion of the full sample size.

Improving the Quality of POCUS use by IM Residents - Focus on Image Archiving

Kolbenson L, Oro A

A key component of a successful Point of Care Ultrasound (POCUS) program is image archiving which facilitates image review and feedback. Internal Medicine (IM) residents use POCUS for procedures and clinical assessment, but few residents archive their images.This quality improvement initiative was developed to increase the number of POCUS images archived by IM residents. Our goals were to have >75% of all non-procedural scans performed by PGY1 IM residents saved and to have > 50% of PGY1 IM residents save at least one scan over the study period.

This Quality Improvement project was conducted on a clinical teaching unit (CTU) with approval from the IM Training Program. Three Plan-Do-Study-Act (PDSA) cycles were carried out over the academic year including: a presentation to PGY1 IM residents highlighting how and why to save POCUS images, the creation and distribution of educational resources for use during clinical work, and finally contacting residents who have not saved scans and asking them to identify barriers they have faced. Outcomes include percentage of non-procedural scans saved by PGY1 IM residents and rate of image archiving amongst these trainees. Data was collected from the creation of an ultrasound sign out sheet located on department machines.

Over 36 weeks, 38 non-procedural scans were performed by PGY1 IM residents on our CTU. The percentage of scans saved was 47%. At least one scan was saved by 75% of residents who used the ultrasound machine.

Prior to this project we have estimated that <10% of all scans performed on our CTU were saved. Though not yet at target, we were able to increase the number of non-procedural scans saved by PGY1 IM residents as well as the number of residents saving scans.

Novel small molecule therapies that inhibit neurodegeneration fill a major therapeutic gap in the treatment of MS.

Levin MC, Salapa HE, Thibault PA, Libner CD, Ding Y, Clarke JPWE, Kalyaanamoorthy S, Ganesan A, Hutchinson C, Hammond SA, Vizeacoumar FS, Alcorn J, Page B

Neurodegeneration, the death and damage to neurons and axons, underlies permanent disability in multiple sclerosis (MS). Yet, regardless of marginal effect on neurodegeneration, immunotherapies are still the primary treatment for MS. We discovered that dysfunction of the RNA binding protein heterogeneous nuclear ribonucleoprotein A1 (A1), including its cytoplasmic mislocalization and aggregation in neurons, drives neurodegeneration in MS and its models. We hypothesize that correcting A1 dysfunction will rescue neurodegeneration in relevant MS models.

Two systems were used to assess A1 dysfunction, including stress-induced A1 dysfunction in primary mouse neurons and optogenetics induced A1 aggregation in a differentiated neuronal cell line. An A1-specific peptide was used to inhibit A1 dysfunction. In silico modeling and thermal shift binding assays were used to model peptide-A1 interactions, which identified small molecules with the potential to inhibit A1 dysfunction. Small molecules were examined for their ability to inhibit A1 dysfunction and neurodegeneration as well as for toxicity and efficacy in mice.

A1 nucleocytoplasmic mislocalization and cytoplasmic A1 aggregation caused decreased neurite length, a marker of neurodegeneration. The A1-specific peptide reduced A1 mislocalization ($p<0.001$) and A1 aggregation ($p<0.0001$) and rescued neurite length ($p<0.001$) in both model systems. In-silico modeling identified three peptidomimetic small molecules that bound A1 and reduced A1 mislocalization ($p<0.001$) and aggregation ($p<0.001$) and rescued neurites ($p<0.01$) like the A1-specific peptide. The small molecule with the greatest in vitro effects was non-toxic and efficacious in mice ($p<0.01$) with MS-like disease.

A1 specific small molecules inhibited A1 dysfunction and ameliorated neurodegeneration, the root cause of disability in MS, thus fulfilling a major therapeutic gap in the treatment of MS.

Thank you for attending the DoM Research Day!