The Twentieth Annual Scientific Meeting for Health Science Research Trainees
Faculty of Health Sciences
Queen's University

Wednesday, May 24th, 2017
Biosciences Complex

Sponsored By

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Laura van Staalduinen, Biomedical and Molecular Sciences

Acknowledgments

A special thank you to Katherine Brennan-Rowcliffe and Alana Korczynski for their invaluable assistance in organizing this meeting.

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Health Science Research Trainees

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Biosciences Complex, Atrium and Room 1101

8:00 - 8:45am	***Registration and A.M. Poster Set-Up (Odd Numbered Abstracts)*** *Biosciences Complex, Atrium*
8:45 - 9:00am	***Introductory Remarks*** Dr. Brian Bennett, Associate Dean, Graduate and Postdoctoral Education, Faculty of Health Sciences Dr. Richard K Reznick, Dean, Faculty of Health Sciences and Director, School of Medicine
9:00 – 9:30am	***Keynote Speaker*** Dr. Amer Johri, MD, MSc, FRCPC, FASE Associate Professor Department of Medicine

"Remarks from the Marine Silk Road:
On a journey of scientific discovery to Guangzhou"

Oral Presentations – Session 1

Chair: Dr. Thomas Massey

Biomedical Engineering

9:35 – 9:47am **COMPUTER-ASSISTED TRAINING AND EVALUATION IN PROCEDURAL SKILL ACQUISITION.** Zsuzsanna Keri MD[1], Tamas Ungi MD PhD[1], Matthew Holden MSc[1], Gabor Fichtinger PhD[1], and Robert McGraw MD Med FRCPC[2] 1 Percutaneous Surgery Laboratory, School of Computing 2 Department of Emergency Medicine, Clinical Simulation Centre (Abstract #2)

Neuroscience Research

9:47 – 9:59am **THE SEARCH FOR EFFECTIVE CORRECTION- SYSTEMIC HEXOSAMINIDASE HYBRID GENE THERAPY ON NEONATAL AND ADULT SANDHOFF MICE.** Karlaina JL. Osmon[1], E. Woodley[2], P. Thompson[3], M. Vyas[1], S. Karumuthil-Melethil[4], John G. Keimel[5], S. J. Gray[4, 6] and J. S. Walia[1, 2, 3*] [1]Centre for Neuroscience Studies, Queen's University, Kingston, Ontario, Canada, K7L 3N6; [2]Department of Biomedical and Molecular Sciences, Queen's University, Kingston, Ontario, Canada, K7L 3N6; [3]Medical Genetics/Departments of Pediatrics, Queen's University, Kingston, Ontario, Canada, K7L 2V7; [4]Gene Therapy Center, University of North Carolina, Chapel Hill, North Carolina, United States; [5] New Hope Research Foundation, North Oaks, Minnesota, USA [6]Department of Ophthalmology, University of North Carolina, Chapel Hill, North Carolina, United States. (Abstract #64)

Cancer Research and Therapy

9:59 – 10:11am **ROLE OF THE PROGRAMMED DEATH LIGAND 1 (PD-L1) IMMUNE CHECKPOINT IN THE ACQUISITION OF MALIGNANT PHENOTYPES IN TUMOUR CELLS**, Minassian Lori.M., Sanwalka D., MacDonald-Goodfellow S., Siemens, D.R. and Graham, C.H. (Abstract #19)

Cardiac, Circulatory, and Reparatory Sciences

10:11 – 10:23am **PDE1C REGULATES THE DYNAMICS OF ACTIN-BASED STRUCTURES IN MIGRATING HUMAN ARTERIAL SMOOTH MUSCLE CELLS**. Paulina Brzezinska[1], Darrin M. Payne[2], Jodi Mackeil[1], Jonah Burke Kleinmann[1], Donald H. Maurice[1]. Department of Biomedical & Molecular Sciences[1] and Department of Surgery[2], Queen's University, Kingston, ON, Canada. (Abstract #25)

10:25 - 10:45am ***Coffee Break***

10:45am - 12:15pm ***A.M. Poster Presentations (Author Attendance)***

12:15 - 1:00pm ***Lunch, A.M. poster tear-down, P.M. poster set-up (Even Numbered Abstracts)***

1:00 - 2:30pm ***P.M. Poster Presentations (Author Attendance), Tear-down***

Oral Presentations – Session 2

Chair: Dr. Peter Greer

Health Policy, Population Health, and Epidemiology

2:30 – 2:42pm **HIGH LEVELS OF SOCIAL AND PHYSICAL INVOLVEMENT IN TEAM SPORT ARE ASSOCIATED WITH ADOLESCENT SUBSTANCE USE BEHAVIORS.** Dylan O'Sullivan, Randy Boyes, Brooke Linden (Abstract #39)

Therapeutics and Toxicology

2:42 – 2:54pm **EFFECTS OF POSTNATAL ADRENERGIC RECEPTOR STIMULATION ON LATENT CONGENITAL HEART DEFECTS IN MALE SPRAGUE DAWLEY RATS.** Rebecca D. Maciver, Michael A. Adams, Louise M. Winn & Terence R. S. Ozolinš. Department of Biomedical and Molecular Sciences, Queen's University, Kingston, ON. (Abstract #79)

Inflammation, Infection and Immunity

2:54 – 3:06pm **IL-30-INDUCED PROINFLAMMATORY CYTOKINE EXPRESSION IS DEPENDENT ON ENGAGEMENT OF THE WSX-1 RECEPTOR IN HUMAN IMMUNE CELLS.** Carlene Petes[1], Mélissa Mariani[2], Yawen Yang[1], Nathalie Grandvaux[2], Katrina Gee[1] [1] Department of Biomedical and Molecular Sciences, Queen's University, Kingston ON, Canada, K7L3N6; [2] Department de biochimie et médicine moléculaire, Université de Montréal, Centre de Recherche du CHUM (CRCHUM), Montréal PQ, Canada, H2X 0A9 (Abstract #43)

Cardiac, Circulatory, and Respiratory Sciences

3:06 – 3:18pm **VASCULAR IMAGING AS A BAROMETER FOR THE EARLY DETECTION OF CARDIOVASCULAR DISEASE (VIBE PROGRAM).** Laura-Eve Mantella, Kayla Colledanchise, Tina Zhu, Joseph Abunassar, Amer Johri Department of Biomedical and Molecular Sciences, Queen's University, Kingston ON (Abstract #26)

3:20 – 3:45pm ***Coffee Break***

Oral Presentations – Session 3

Chair: Dr. Mark Ormiston

Cancer Research and Therapy

3:45 – 3:57pm **EPIGENETIC, STRUCTURAL, AND FUNCTIONAL CHARACTERIZATION OF THE E2A-PBX1 ONCOGENIC TRANSCRIPTIONAL NETWORK**. Marina R. Lochhead, David N. Langelaan, Kyster Nanan, Steven P. Smith, David P. LeBrun (Abstract #20)

Neurosciences Research

3:57 – 4:09pm **EXAMINING THE EFFECT OF DOPAMINERGIC TREATMENT ON COGNITIVE FUNCTION IN PARKINSON'S PATIENTS DURING AN OCULOMOTOR STRATEGIC DECISION-MAKING TASK.** Parr, Ashley, Riek, H., Coe, B., Pari, G., & Munoz, D.(Abstract #65)

Protein Structure and Function

4:09 – 4:21pm **SOLUTION CHARACTERIZATION OF THE COHESIN-DOCKERIN DUAL BINDING MODE: A HIGH AFFINITY PROTEIN-PROTEIN INTERACTION CRITICAL FOR CELLULOSOME ASSEMBLY.** Alison L. Upsdell, Holly L. Spencer, David N. Langelaan, Steven P. Smith (Abstract #72)

Inflammation, Infection and Immunity

4:21 – 4:33pm **CELLULAR AND MOLECULAR MECHANISMS INVOLVED IN INFLAMMATORY PAIN.** Jaqueline Silva, Jelena Petrovic, Ian Gilron, Nader Ghasemlou Department of Biomedical and Molecular Sciences (Abstract #44)

4:35 – 4:45pm ***Awards and Concluding Remarks***

5:00 – 7:00pm ***Reception at the Grad Club***
162 Barrie Street
Cash Bar/ Non-Alcoholic Punch
Hors d'oeuvres

Poster Presentations

Biomedical Engineering

COMPARISON OF 3D ULTRASOUND TO COMPUTER TOMOGRAPHY IN KNEE OSTEOPHYTE DEPICTION: VALIDATION OF RESEARCH PROTOCOL. Valeria Vendries, Tamas Ungi, Leslie MacKenzie, Gabriel Venne. Department of Biomedical and Molecular Sciences, Queens University. (Abstract #1)

Cancer Research and Therapy

CHEMOTHERAPY-SENSITIZING EFFECTS OF ASPIRIN, METFORMIN, AND OSELTAMIVIR PHOSPHATE IN PANCREATIC CANCER. Bessi Qorri[1], Manpreet Sambi[1], William Harless[2], Myron R Szewczuk[1] [1]Department of Biomedical and Molecular Sciences, Queen's University, Kingston, Ontario, Canada [2]ENCYT Technologies, Inc., Membertou, Nova Scotia, Canada (Abstract #3)

ROLE OF PPARγ-DEPENDENT MICRORNA EXPRESSION DURING BREAST TUMOUR METASTASIS Bradley J. Ross[1], Rachel E. Rubino[2] and Christopher J.B. Nicol[1-3]. Dept. of [1]Pathology & Molecular Medicine; [2]Division of Cancer Biology & Genetics, Cancer Research Institute; [3]Dept. of Biomedical & Molecular Sciences, Queen's University, Kingston, ON, Canada K7L 3N6. (Abstract #4)

TUMOUR CELL DRUG RESISTANCE INDUCED BY THE PROGRAMMED DEATH LIGAND 1 (PD-L1) IMMUNE CHECKPOINT IS ASSOCIATED WITH AUTOPHAGY. Sanwalka, D., Minassian L.M., Macdonald-Goodfellow S.K., Siemens, D.R. and Graham, C.H. Biomedical and Molecular Sciences (Abstract #5)

CLONAL HEMATOPOIESIS OF AGING IS ASSOCIATED WITH SPECIFIC IMMUNOLOGICAL PARAMETERS AND CLINICAL COMORBIDITIES: TOWARDS PRACTICAL SCREENING IN OLDER ADULTS. Elina K. Cook[1], Terumi Izukawa[2], Dylan Johnson[1], Eva Bain[1], Jamie Hilland[1], Brooke Snetsinger[1], Bushra Momtaz[2], Janika Francis[3], Sherylan Young[3], Gili Rosen[2], Mina Jamali[3], Jonah Buckstein[1], Rena Buckstein[3] and Michael Rauh[1] [1]Department of Pathology and Molecular Medicine, Queen's University, Kingston, Canada [2]Baycrest Health Sciences, Toronto, Canada [3]Odette Cancer Centre, Sunnybrook Health Sciences, Toronto, Canada (Abstract #6)

ANTICANCER ACTIVITIES OF PPARg IN HER2+ BREAST CANCER. Lightbody Elizabeth D.[1], O'Connell Katie M.[2], Rubino Rachel E.[2], Apostoli Anthony J.[2], SenGupta Sandip K.[1], and Nicol Christopher JB.[1-3] [1]Departments of Pathology and Molecular Medicine; [2]Cancer Biology and Genetics, Cancer Research Institute; and [3]Biomedical and Molecular Sciences, Queen's University, Kingston, ON, Canada (Abstract #7)

THE ROLE OF STAT1 IN MODULATION OF THE TUMOUR IMMUNE MICROENVIRONMENT AND RESPONSE TO CHEMOTHERAPY IN HIGH-GRADE SEROUS OVARIAN CANCER. Gillian Reid-Schachter, Nichole Peterson, Charles Graham, Runhan Ren, Peter Truesdell, Julie Francis, Andrew Craig, Madhuri Koti. Department of Biomedical and Molecular Sciences/Cancer Biology and Genetics Division/Queen's Cancer Research Institute/Queen's University, Department of Pathology and Molecular Medicine & Department of Obstetrics and Gynecology/Kingston General Hospital (Abstract #8)

INBUILT SUICIDAL MECHANISM AS A SAFETY CHECK FOR LONG TERM GENE THERAPY STUDIES. Imtiaz Ahmad[1], Shalini Kot[1], [1]Evan Woodley, Meera Vyas[2], Karlaina Osmon[2], Sabrina Quazi[3], Zhilin Chan[4], Patrick Thompson[4] and Jagdeep S Walia[4] [1]Department of Biomedical and Molecular Sciences, [2]Centre for Neuroscience studies, [3]Department of biomedical computing and [4]Medical Genetics/Department of Pediatrics, Queen's University, Kingston, Ontario, Canada, K7L 2V7. (Abstract #9)

GENETIC MODELING OF CALPAIN-1/2 AS THERAPEUTIC TARGETS IN BREAST CANCER. James A. MacLeod, Yan Gao, Chris Hall, and Peter A. Greer. Department of Pathology & Molecular Medicine, Queen's University, Division of Cancer Biology and Genetics, Cancer Research Institute, Kingston, Ontario, Canada. (Abstract #10)

EVALUATION OF DRUG RESISTANCE TRANSFER VIA EXTRACELLULAR VESICLES IN HUMAN OVARIAN CANCER CELLS. Jennifer F. Power & Susan P.C. Cole Pathology & Molecular Medicine (Abstract #11)

A BREAST TUMOUR ANGIOGENIC ROLE FOR PPARγ SIGNALING. Jia Yue (Amelia) Shi[1], Anthony J. Apostoli[2], Rachel E. Rubino[3] and Christopher J.B. Nicol[1-31]Depts. of Biomedical & Molecular Sciences, Queen's University, Kingston, ON, Canada[2]Pathology & Molecular Medicine, Queen's University, Kingston, ON, Canada [3]Division of Cancer Biology & Genetics, Cancer Research Institute; Queen's University, Kingston, ON, Canada (Abstract #12)

EVALUATING PROPHYLACTIC VACCINATION MODELS TO ASSESS TUMORIMMUNE CELL INTERACTIONS FOLLOWING TUMOR ENGRAFTMENT. Kyle Seaver[2], Peter Greer[1] and Sam Basta[2]. [1]Division of Cancer Biology and Genetics, Cancer Research Institute, Department of Pathology and Molecular Medicine, Queen's University, Kingston, Ontario, Canada. [2]Department of Biomedical & Molecular Science Queen's University, Kingston, Ontario, Canada. (Abstract #13)

CO-EXPRESSION GENE NETWORKS ASSOCIATED WITH THERAPEUTIC RESPONSE IN OVARIAN CANCER. Jihoon Choi[1] , Anastasiya Tarnouskaya[2] , Matt Nevile[1] , Margot Gunning[1] , Madhuri Koti[1] , Qingling Duan[1,2] [1]Department of Biomedical and Molecular Sciences, Queen's University, [2]School of Computing, Queen's University (Abstract #14)

SENSITIZING DORMANT PANCREATIC AND BREAST CANCER STEM CELLS WITH INTERLEUKIN-6 AND HEPATOCYTE GROWTH FACTOR FOR TARGETED MULTIMODAL CHEMOTHERAPY. Manpreet Sambi*[1], William Harless[2], Myron R Szewczuk[1] [1]Department of Biomedical and Molecular Sciences, Queen's University, Kingston, Ontario, Canada [2]ENCYT Technologies, Inc., Membertou, Nova Scotia, Canada (Abstract #15)

***PTEN* ASSOCIATED TYPE 1 INTERFERON RESPONSE IN PROSTATE CANCER CELLS.** Natasha Vitkin, Abdi Ghaffari, Nichole Peterson, Robert Siemens, Madhuri Koti Department of Biomedical and Molecular Sciences/Cancer Biology and Genetics Division/Queen's Cancer Research Institute/Queen's University, Department of Urology & Department of Obstetrics and Gynecology/Kingston General Hospital (Abstract #16)

SIALYLATION OF CELL SURFACE GLYCOPROTEINS FACILITATES FORMATION OF 3D MULTICELLULAR PROSTASPHERES BY ENHANCING CELL-CELL ADHESION, THEREBY PREVENTING DISSEMINATION OF METASTATIC CELLS. Sabah Haq, Vanessa Samuel, and Myron Szewczuk. Department of Biomedical and Molecular Sciences, Queen's University, Kingston, Ontario, Canada. (Abstract #17)

RET-MEDIATED INVASION IN THREE-DIMENSIONAL MICROENVIRONMENT MODELS. Sarah m. Maritan, Eric Y. Lian, and Lois M. Mulligan Department of Pathology & Molecular Medicine; Queen's Cancer Research Institute Division of Cancer Biology and Genetics, Queens's University, Kingston, ON. (Abstract #18)

Cardiac, Circulatory, and Respiratory Sciences

ALTERING ACTIVE VITAMIN D_3 SUPPLEMENTATION IN EXPERIMENTAL CKD, IRRESPECTIVE OF CHANGES TO CIRCULATING PTH, DO NOT MITIGATE THE DEVELOPMENT OF VASCULAR DISEASE. Svajger B[1]., Pruss C[1]., Laverty K[1]., Zelt .G.E[3]., Petkovich, M[1]., Holden R.M[2]., Adams M.A.A[1]. [1]Department of Biomedical and Molecular Sciences, Queen's University, Kingston, ON; [2]Department of Medicine Queen's University, Kingston, ON; [3]Department of Medicine, University of Ottawa, Ottawa, ON. (Abstract #21)

FEMORAL PLAQUE QUANTIFICATION BY TWO-DIMENSIONAL ULTRASOUND FOR THE PREDICTION OF CORONARY ARTERY DISEASE. Kayla Colledanchise, Laura Mantella, Marie-France Hétu, Milena Bullen, Julia Herr, Joseph Abunassar, Amer Johri. Department of Biomedical and Molecular Sciences. Queen's University, Kingston, Ontario Canada. (Abstract #22)

SENSORY-MECHANICAL RESPONSES TO HIGH-DOSE METHACHOLINE BRONCHOPROVOCATION IN HEALTHY NORMAL SUBJECTS. Nilita Sood[1], Thomas Fisher[1], Taylar Wall[1], John T. Fisher[1], and M. Diane Lougheed[1]. [1]Department of Biomedical and Molecular Sciences, Queen's University, Kingston, ON. (Abstract #23)

IN VIVO CHARACTERIZATION OF A TWO NOVEL MUSCARINIC RECEPTOR 3 (MR3) ANTAGONISTS: ABH 423 AND JHH 378. S. Vincent[1], K., Kobilka[2], H., Wess[4], J., Gmeiner[3], P. and Fisher[1], J.T. Department of Biomedical and Molecular Sciences, Queen's University[1], Kingston, Ontario, Canada; Department of Molecular and Cellular Physiology, Stanford University School of Medicine[2], Stanford, California, U.S.A; Molecular Signaling Section, Laboratory of Bioorganic Chemistry, National Institute of Diabetes and Digestive and Kidney Diseases[4], Bethesda, Maryland, U.S.A; and Department of Chemistry and Pharmacy, Friedrich Alexander University[3], Erlangen, Germany. (Abstract #24)

VON WILLEBRAND FACTOR REGULATES DEEP VEIN THROMBOSIS IN A MOUSE MODEL OF DIET-INDUCED OBESITY. Alison Michels[1], Courtney N. Dwyer[1], Laura L. Swystun[1] and David Lillicrap[1] [1]Department of Pathology and Molecular Medicine, Queen's University (Abstract #27)

Health Policy, Population Health, and Epidemiology

HEARING TESTING AND EAR TUBES IN ONTARIO - A CHANGING LANDSCAPE. Jason A. Beyea MD PhD FRCSC, Trina Stephens MSc, Emily Rosen MClSc, and Steve Hall MD MSc FRCSC. Department of Otolaryngology, Hotel Dieu Hospital, Queen's University, Kingston, Ontario, Canada. (Abstract #28)

A POPULATION-BASED STUDY OF PATIENT AND SYSTEM FACTORS ASSOCIATED WITH ADVANCED CUTANEOUS MELANOMA IN ONTARIO. Mavor, M.E.[1,2], Richardson, H.[1,2,3], Miao, G.[1], Hanna, T.P.[1,4,5] 1.Division of Cancer Care and Epidemiology, Cancer Research Institute at Queen's University, 10 Stuart Street, 2nd Level, Kingston ON K7L3N6 Canada 2.Department of Public Health Sciences, Queen's University, Kingston ON K7L3N6 3.Canadian Cancer Trials Group, Cancer Research Institute at Queen's, 10 Stuart Street, Level 1, Kingston ON K7L3N6 4.Department of Oncology, Queen's University, 76 Stuart Street, Kingston ON K7L2V7 5.Institute for Clinical Evaluative Sciences at Queen's University, 21 Arch Street, Kingston ON K7L3L4 (Abstract #29)

ASSOCIATION BETWEEN THE UGT2B17 GENE DELETION AND WORSENED VASOMOTOR QUALITY OF LIFE IN POSTMENOPAUSAL WOMEN PARTICIPATING ON THE MAP.3 PREVENTION TRIAL. Braden Knight, Philip Lazarus, Thomas Massey and Harriet Richardson. Department of Public Health Sciences, Queen's University Kingston, Ontario, Canada (Abstract #30)

THE ROLE OF OUTDOOR PLAY AND NATURE CONNECTEDNESS IN THE OCCURRENCE OF PSYCHOSOMATIC SYMPTOMS AMONG CANADIAN ADOLESCENTS. Caroline Piccininni and William Pickett. Department of Public Health Sciences, Queen's University, Kingston, Ontario, Canada. (Abstract #31)

MORTALITY PATTERNS AMONG ONTARIANS WITH INTELLECTUAL AND DEVELOPMENTAL DISABILITIES. Elizabeth Stankiewicz, Micheal McIsaac, Helene Ouellette-Kuntz, Department of Public Health Sciences Queen's University, Kingston, Ontario (Abstract #32)

NEIGHBOURHOOD WALKABILITY AND OBJECTIVELY MEASURED ACTIVE TRANSPORTATION AMONG 10-13 YEAR OLDS. Gillian Williams; Dr. Ian Janssen, Department of Public Health Sciences (Abstract #33)

INVESTIGATING CORTISOL PRODUCTION, PATTERN AND VARIABILITY AS MEDIATORS IN THE RELATIONSHIP BETWEEN SHIFT WORK AND METABOLIC SYNDROME. Jennifer Ritonja[1], Kristan J. Aronson[1,2], Jill Korsiak[3], Andrew Day[4], Joan Tranmer[1,5] [1]Department of Public Health Sciences, Queen's University, Kingston, Canada [2]Divison of Cancer Care and Epidemiology, Cancer Research Institute, Queen's University, Kingston, Canada [3]Research Institute and Centre for Global Child Health, Peter Gilgan Centre for Research and Learning, The Hospital for Sick Children, Toronto, Canada [4]Clinical Research Centre, Kingston General Hospital, Kingston, Canada [5]School of Nursing, Queen's University, Kingston, Canada (Abstract #34)

SHIFT WORK PATTERNS, CHRONOTYPE, AND OVARIAN CANCER RISK. Leung L[1,3], Grundy A[1,2], Aronson KJ[3,4], Koushik A[1,2] Université de Montréal Hospital Research Centre (CRCHUM), 850 Saint-Denis Street, 2nd Floor, Montreal, QC H2X 0A9, Canada, Department of Social and Preventative Medicine, Université de Montréal, Montreal, Quebec, Canada.Department of Public Health Sciences, Queen's University, Kingston ON K7L3N6 Division of Cancer Care and Epidemiology, Queen's Cancer Research Institute, Queen's University, Kingston, Ontario, Canada (Abstract #35)

EXPLORING EXPECTATIONS OF PUBLIC STIGMA AS A MEDIATOR IN THE RELATIONSHIP BETWEEN OCCUPATIONAL PRESTIGE AND PROFESSIONAL MENTAL HEALTH CARE SEEKING IN THE GENERAL CANADIAN POPULATION. Lyndsey A. Telega. Department of Public Health Sciences, Queen's University, Kingston, Ontario, Canada. (Abstract #36)

LIFETIME CAFFEINE INTAKE AND THE RISK OF EPITHELIAL OVARIAN CANCER. Simran K. Sandhu, Anne Grundy, Kristan J. Aronson, & Anita Koushik. Department of Public Health Sciences, Queen's University, Kingston, Ontario, Canada**.** (Abstract #37)

ASSOCIATION BETWEEN TUMOR SIZE AND SURVIVAL IN PATIENTS WITH SURGICALLY RESECTED INTRAHEPATIC CHOLANGIOCARCINOMA IN ONTARIO. Suriya J. Aktar, Harriet Richardson, Jina Zhang-Salomons, Sulaiman *Nanji,* Christopher M. *Booth,* and Jennifer A. Flemming. Cancer Care & Epidemiology, Queen's Cancer Research Institute, Queen's University, Kingston, Ontario, Canada. (Abstract #38)

Inflammation, Infection and Immunity

γδ T CELL CONTROL OF INFLAMMATORY PAIN. Jelena Petrovic[1], Jaqueline Silva[1,2] and Nader Ghasemlou[1,2] Department of [1]Biomedical and Molecular Sciences and [2]Anesthesiology and Perioperative Medicine, Queen's University, Kingston, ON, Canada (Abstract #40)

INVESTIGATING THE EFFECTS OF IL-27 ON ENDOSOMAL TOLL-LIKE RECEPTOR EXPRESSION AND ACTIVATION IN HUMAN MONOCYTES AND MACROPHAGES. Natalya Odoardi[1], Carlene Petes[1], Katrina Gee[1]. [1]Department of Biomedical and Molecular Sciences, Queen's University, Kingston, ON. (Abstract #41)

NASAL AND PERIPHERAL BLOOD GROUP 2 INNATE LYMPHOID CELL (ILC2) LEVELS IN RESPONSE TO NASAL ALLERGEN CHALLENGE IN PARTICIPANTS WITH ALLERGIC RHINITIS. Mark W. Tenn[1], Jenny Thiele[1,2], Anne K. Ellis[1,2,3] [1] Department of Biomedical and Molecular Sciences, Queen's University, Kingston, Ontario, Canada [2] Allergy Research Unit, Kingston General Hospital, Kingston, Ontario, Canada [3] Division of Allergy & Immunology, Department of Medicine, Queen's University, Kingston, Ontario, Canada (Abstract #42)

Neuroscience Research

A MULTI-MODAL IMAGING APPROACH TO ASSESS THE RELATIONSHIP BETWEEN STRUCTURAL AND PHYSIOLOGICAL CHANGES FOLLOWING SPORT CONCUSSION. Allen A. Champagne**,** BSc, BA, Nicole S. Coverdale, PhD, Stephen H. Scott, PhD, Clarisse I. Mark, PhD, Douglas J. Cook, MD, PhD. Centre for Neuroscience Studies, Queen's University, Kingston, Ontario, Canada. (Abstract #45)

THE PADS STUDY: PROBIOTICS ALLEVIATING DEPRESSIVE SYMPTOMS. Caroline Wallace[1], Jane Foster[2,3], Sidney H. Kennedy[3], & Roumen Milev[1,4] [1]Centre for Neuroscience Studies, Queen's University; [2]Department of Psychiatry and Behavioural Neurosciences, McMaster University; [3]University Health Network; [4]Department of Psychiatry, Queen's University. (Abstract #46)

CHARACTERIZATION OF THE INFLUENCE OF CIRCADIAN RHYTHMS ON SOMATOSENSATION. Kaitlyn Tresidder, Julia Segal, Ian Gilron, Nader Ghasemlou. Centre for Neuroscience Studies, Department of Biomedical and Molecular Sciences, and Department of Anesthesiology, Queen's University, Kingston, ON, Canada (Abstract #47)

IMMUNOHISTOCHEMICAL CHARACTERIZATION OF SENSORY NEURONS SURROUNDED BY POSTGANGLIONIC SYMPATHETIC BASKETS IN THE MOUSE TRIGEMINAL GANGLIA. Hanin Alsaadi (Ph.D. Candidate), Nader Ghasemlou and Michael D. Kawaja Centre for Neuroscience Studies, Queen's University, Kingston, Ontario (Abstract #48)

OLFACTORY FUNCTIONING IN DEPRESSION AND THE EFFECTS OF TRANSCRANIAL MAGNETIC STIMULATION Hannah C. Taalman,[1]., Roumen Milev.[2] [1] Centre for Neuroscience Studies, Queen's University, Kingston, ON [2] Department of Psychiatry, Queen's University, Kingston, ON (Abstract #49)

VISUAL SALIENCY RESPONSE IN THE SUPERFICIAL AND INTERMEDIATE SUPERIOR COLLICULUS. Janis Kan , Dr. Laurent Itti , Dr. Douglas Munoz (Abstract #50)

INVESTIGATING PUPIL DYNAMICS IN PATIENTS WITH NEURODEGENERATIVE DISEASES. Jeff Huang, Brian C Coe, Matthew Smorenburg, Donald Brien, Sandra Black, Liz Finger, Morris Freedman, Tony Lang, Tanya Schmah, Rick Swartz, Carmela Tartaglia, Lorne Zinman, Douglas P Munoz, and the ONDRI Investigators (Abstract #51)

QUANTIFYING SENSORIMOTOR AND VISUOSPATIAL IMPAIRMENTS IN CHRONIC KIDNEY DISEASE PATIENTS: A PILOT STUDY. Jessica Vanderlinden, Dr. Stephen Scott PhD, Dr. Rachel Holden MSc, MD, and Dr. J. Gordon Boyd, MD, PhD Centre for Neuroscience Studies, Queen's University Kingston, Ontario Canada. (Abstract #52)

BRAIN TISSUE OXYGENATION AND QUANTIFIED NEUROLOGICAL OUTCOMES IN PATIENTS UNDERGOING CORONARY ARTERY BYPASS SURGERY. Joanna S. Semrau BSc, Stephen H. Scott PhD, Andrew G. Hamilton MD, Dimitri Petsikas MD, Darrin Payne MD, Gianluigi Bisleri MD, Tarit Saha MD, and J. Gordon Boyd MD PhD Centre for Neuroscience Studies (Abstract #53)

THE ROLE OF DIFFERENTIAL NA+/K+ PUMP ISOFORM EXPRESSION IN HIGHER AND LOWER BRAIN REGIONS AND CONSEQUENCES FOR ISCHEMIA. Chloe Lowry, Michael Golod, Brian Bennett, R. David Andrew. Centre for Neuroscience Studies, Queen's University, Kingston, ON, Canada (Abstract #54)

USING ADENO-ASSOCIATED VIRUS SEROTYPE 9 TO TREAT GM2 ACTIVATOR PROTEIN DEFICIENCY IN A MOUSE MODEL Meera Vyas[1], K. Osmon[1], I. Ahmad[2], S. Kot[2], P. Thompson[3], S. J. Gray[4, 5] and J. S. Walia[1, 2, 3*1]Centre for Neuroscience Studies, Queen's University, Kingston, Ontario, Canada, K7L 3N6; [2]Department of Biomedical and Molecular Sciences, Queen's University, Kingston, Ontario, Canada, K7L 3N6; [3]Medical Genetics/Departments of Pediatrics, Queen's University, Kingston, Ontario, Canada, K7L 2V7; [4]Gene Therapy Center, University of North Carolina, Chapel Hill, North Carolina, United States; [5]Department of Ophthalmology, University of North Carolina, Chapel Hill, North Carolina, United States. (Abstract #55)

LOW BRAIN TISSUE OXYGENATION CONTRIBUTES TO THE DEVELOPMENT DELIRIUM DURING CRITICAL ILLNESS. Michael D. Wood, BA.[1]; David M. Maslove, MSc, MD[2,3]; John G. Muscedere, MD[2]; Andrew G. Day, MSc[4]; J. Gordon Boyd, MD, PhD[1,2,3] [1]Centre for Neuroscience Studies, Queen's University, Kingston, ON, Canada; [2]Dept. of Critical Care Medicine, Queen's University, Kingston, ON, Canada; [3]Dept. of Medicine, Queen's University, Kingston, ON, Canada; [4]Kingston General Hospital Research Institute, Kingston, ON, Canada (Abstract #56)

THE PRO-INFLAMMATORY CYTOKINE TUMOR NECROSIS FACTOR ALPHA EXCITES SUBFORNICAL ORGAN NEURONS. Nick J. Simpson[1,2], Alastair V. Ferguson[1,2] (Abstract #57)

OXIDATIVE STRESS AND CHRONIC UNPREDICTABLE STRESS INTERACTIONS IN A MODEL OF PROGRESSIVE NEURODEGENERATION AND NEUROPSYCHIATRIC COMORBIDITIES. Nicole Czegledy and Brian Bennett. Centre for Neuroscience Studies. Queen's University Kingston, Ontario. (Abstract #58)

USING AN EMOTIONAL SACCADE TASK TO ESTABLISH BEHAVIOURAL BIOMARKERS IN ATTENTION-DEFICIT HYPERACTIVITY DISORDER AND BIPOLAR DISORDER. Rachel Yep, Donald C. Brien, Brian C. Coe, Alina Marin & Douglas P. Munoz Centre for Neuroscience Studies, Queen's University, Kingston, ON Canada (Abstract #59)

STRUCTURE AND TIMING OF COMPUTERIZED COGNITIVE TRAINING TASKS IN SCHIZOPHRENIA: AN EEG ANALYSIS. Robyn Cardy, MSc Candidate; Dr. Felicia Iftene, MD, PhD, FRCPC (Abstract #60)

INVESTIGATING THE EFFECTS OF RAPAMYCIN AND PREDNISONE ON THE HEIGHTENED IMMUNE RESPONSE FOLLOWING AAV9-HEXM TREATMENT IN SANDHOFF MICE. Shalini Kot, K.J.L. Osmon, E. Woodley, P. Thompson, M. Vyas, I. Ahmad, Z. Chen, M. Mitchell and J.S. Walia (Abstract #61)

AN EVALUATION OF A STIGMA MANAGEMENT PSYCHOEDUCATIONAL AND BEHAVIOURAL MODIFICATION COURSE FOR PEOPLE WITH MOOD AND ANXIETY DISORDERS. Shamik Sen and Roumen Milev. Department of Neuroscience, Queen's University Kingston, Ontario Canada. (Abstract #62)

SPREADING DEPOLARIZATION EVOKED BY OXYGEN-GLUCOSE DEPRIVATION IN CEREBRAL CORTICAL SLICES OF THE FROG. V. Donovan, R.D. Andrew. Centre for Neuroscience Studies (Abstract #63)

Other

USE OF ANIMATIONS AS AN ACTIVE TEACHING TOOL IN DEVELOPMENTAL ANATOMY. Sidra Shafique, Ron A. Easteal, Conrad Reifel. Department of Biomedical and Molecular Sciences, Faculty of Health Sciences, Queen's University, Kingston, Ontario, Canada. (Abstract #66)

MISSING DATA IN COMPLEX SURVEYS: AN OVERIVEW OF MULTIPLE IMPUTATION AND WEIGHTED APPROACHES. Michael A. Reaume and Michael A. McIsaac**.** Department of Public Health Sciences, Queen's University**,** Kingston, Ontario, Canada (Abstract #67)

EVALUATION OF A WEB-BASED MODULE AND AN OTOSCOPY SIMULATOR IN TEACHING EAR DISEASE. Vincent, Wu BHSc[1] and Jason A. Beyea MD PhD FRCSC[1 1]Department of Otolaryngology, Hotel Dieu Hospital, Queen's University, Kingston, Ontario. Queen's University Clinical Simulation Centre (Abstract #68)

Protein Structure and Function

FUNCTIONAL ANALYSIS OF THE REGIONS CONNECTING THE MEMBRANE SPANNING DOMAINS TO THE NUCLEOTIDE BINDING DOMAINS OF MRP1. Emma E. Smith, Gwenaëlle Conseil and Susan P.C. Cole. Department of Pathology and Molecular Medicine (Abstract #69)

NON-SYNONYMOUS VARIANTS OF THE HUMAN ORGANIC ANION TRANSPORTER MRP4 (*ABCC4*) IMPAIR PROTEIN LEVELS AND TRAFFICKING TO THE PLASMA MEMBRANE. Gwenaëlle Conseil[1], Katrin Ziems[1], Mayukh Banerjee[2], Elaine M. Leslie[2] & Susan P.C. Cole[1 1] Div of Cancer Biology & Genetics, Queen's University Cancer Research Institute, Kingston, ON [2] Dept of Physiology, University of Alberta, Edmonton, AB (Abstract #70)

ENGINEERING A MULTI-ENZYME COMPLEX WITH ENHANCED AGAROSE-DEGRADING PROPERTIES USING CARBOHYDRATE-ACTIVE ENZYMES. Keegan B. Turner-Wood, Steven P. Smith. Department of Biomedical and Molecular Sciences (Abstract #71)

Reproductive and Sexual Function

EFFECT OF CORM-A1 ADMINISTRATION ON PLACENTAL HYPOXIA LEVELS IN CD-1 MICE. Megan Dickson (B.Sc. Candidate)[1], Karalyn McRae[1], Nichole Peterson[1], Graeme Smith[1,2]. [1]Department of Biomedical and Molecular Sciences, Queen's University, Kingston, Ontario [2]Department of Obstetrics and Gynaecology, Kingston General Hospital, Kingston, Ontario (Abstract #73)

Therapeutics and Toxicology

A NEW TREATMENT PARADIGM FOR NEURODEGENERATION: ISOTOPE-REINFORCED POLYUNSATURATED FATTY ACIDS MITIGATE COGNITIVE IMPAIRMENT IN A MOUSE MODEL OF SPORADIC ALZHEIMER'S DISEASE. Ahmed Elharram[1], Nicole Czegledy[1], Michael Golod[1], Ginger L.Milne[2], Erik Pollock[3], Mikhail S. Shchepinov[4], and Brian Bennett[1]. Department of Biomedical and Molecular Sciences and Centre for Neuroscience Studies, Queen's University, Kingston Ontario Canada[1]; Vanderbilt University, Nashville, TN[2]; University of Arkansas, Fayetteville, AR[3]; Retrotope, Inc. Los Altos, CA[4] (Abstract #74)

HISTOLOGICAL ANALYSIS TO EXPLAIN POOR CARDIOVASCULAR OUTCOMES IN RESPONSE TO LOW DOSE ISOPROTERENOL. Ana Nikolovska, Terence R.S. Ozolinš, & Louise M. Winn. Department of Biomedical and Molecular Sciences, Queen's University, Kingston, ON. (Abstract #75)

THERAPEUTIC IMPACT OF FERMAGATE ON VASCULAR CALCIFICATION IN A RAT MODEL OF CHRONIC KIDNEY DISEASE. Jeronimo PS[1], Pruss C[1], Laverty K[1], Svajger B[1], Turner M[1], Ward E[1], Petkovich M[1], Holden RM[2], Adams MA[1] Department of Biomedical and Molecular Sciences (1) and Department of Medicine (2), Queen's University, Kingston, Ontario, Canada (Abstract #76)

EMBRYOPATHIES INDUCED BY *IN VIVO* VALPROIC ACID EXPOSURE TO MURINE EMBRYOS. Sidra Shafique[1], Louise M. Winn[1,2]. Department of Biomedical and Molecular Sciences, Queen's University, Kingston[1] School of Environmental Studies, Queen's University, Kingston[2] (Abstract #77)

INVESTIGATING PERTURBATIONS OF FETAL TOPOISOMERASE IIA FOLLOWING BENZENE EXPOSURE. Trent H. Holmes and Louise M. Winn. Department of Biomedical and Molecular Sciences, Queen's University Kingston, Ontario Canada (Abstract #78)

Women's and Children's Health Research

MENADIONE AS AN ALTERNATIVE METHOD OF ENDOGENOUS CARBON MONOXIDE PRODUCTION IN MICE. Chioma U Odozor[1], Nichole Peterson[1] and Graeme N Smith[1,2]. [1]Department of Biomedical and Molecular Sciences, Queen's University, Kingston, Ontario, Canada and [2]Department of Obstetrics and Gynecology, Kingston General Hospital, Kingston, Ontario, Canada. (Abstract #80)

CORM-A1 TREATMENT LEADS TO INCREASED BLOOD CARBOXYHEMOGLOBIN IN PREGNANT CD-1 MICE. Karalyn E McRae[1], Nichole Peterson[1] and Graeme N Smith[1,2]. [1]Department of Biomedical and Molecular Sciences, Queen's University, Kingston, Ontario, Canada and [2]Department of Obstetrics and Gynecology, Kingston General Hospital, Kingston, Ontario, Canada. (Abstract #81)

Abstracts

Biomedical Engineering

1. **COMPARISON OF 3D ULTRASOUND TO COMPUTER TOMOGRAPHY IN KNEE OSTEOPHYTE DEPICTION: VALIDATION OF RESEARCH PROTOCOL.** Valeria Vendries, Tamas Ungi, Leslie MacKenzie, Gabriel Venne. Department of Biomedical and Molecular Sciences, Queens University.

   Introduction: Osteophytes (marginal bony outgrowths) are a common radiographic marker of osteoarthritis (OA) and joint degeneration[1]. However, osteophytes are not accurately depicted using conventional imaging modalities[1,2]. This represents problems for evaluating the anatomical changes of the osteoarthritic joint, and for the design of surgical interventions that rely on the accuracy of pre-operative images[2,3]. Studies have shown that ultrasound is a promising tool to detect articular changes such as the presence of osteophytes, and to monitor the progression of OA[1,4]. Furthermore, 3D ultrasound (3DUS), a tool for volume rendering and surface representation[5], can potentially offer a means to quantify and depict osteophytes. Purpose: To establish a research protocol for the comparison of osteophyte depiction in the knee joint using 3DUS and conventional Computed Tomography (CT). Method: 3DUS, CT, and Structured Light Scanner (SLS) images from a distal femur sawbone were obtained, segmented and saved as an .stl model format. Using a custom software, surface matching and Root Mean Square Error (RMSE) analyses were performed to assess the accuracy of each of the evaluated modalities in capturing the anatomy of the bone surface. 3DUS and CT models were compared to the SLS model, which was used as ground truth. Conclusion: We expect to use this protocol design for future comparison studies of the specified imaging modalities for osteophyte depiction on human cadaveric knees with signs of OA.

2. **COMPUTER-ASSISTED TRAINING AND EVALUATION IN PROCEDURAL SKILL ACQUISITION.** Zsuzsanna Keri MD[1], Tamas Ungi MD PhD[1], Matthew Holden MSc[1], Gabor Fichtinger PhD[1], and Robert McGraw MD Med FRCPC[2] 1 Percutaneous Surgery Laboratory, School of Computing 2 Department of Emergency Medicine, Clinical Simulation Centre

   Medical education is undergoing a transformation with the move to competency-based curricula. Simulation-based training is playing a pivotal role in this transformation as it enables high volume repetitive practice without putting patients at risk of complications at the hands of novices. Our research supports the transition to competency-based medical education by providing objective data that enables medical educators to determine the volume and type of practice in the simulated setting that leads to competency in the real clinical environment. The Perk Tutor is a computer assisted training platform developed at Queen's University and used in a collaboration between the School of Computing and the Faculty of Health Sciences. It has been shown to benefit learning in learning image interpretation and interventional skills. Perk Tutor has been shown to be especially useful in teaching ultrasound-guided percutaneous procedures such as central venous catheterization or US-guided lumbar puncture. Recently, in collaboration with the Clinical Simulation Centre, we have developed a curriculum for ultrasound-guided central line placement and evaluated its effectiveness using hand motion analysis (HMA). This approach has enabled medical educators to determine the volume of practice required to achieve competency in this skill. Our objective is to develop, implement and evaluate computer-assisted training platforms that will support medical trainees as they learn procedural skills. We propose that computer assisted training will be a vital link in the transition to competency based medical education and will guide the rational, effective and efficient use of teaching resources.

Cancer Research and Therapy

3. **CHEMOTHERAPY-SENSITIZING EFFECTS OF ASPIRIN, METFORMIN, AND OSELTAMIVIR PHOSPHATE IN PANCREATIC CANCER.** Bessi Qorri[1], Manpreet Sambi[1], William Harless[2], Myron R Szewczuk[1] [1]Department of Biomedical and Molecular Sciences, Queen's University, Kingston, Ontario, Canada [2]ENCYT Technologies, Inc., Membertou, Nova Scotia, Canada

Pancreatic ductal adenocarcinoma (PDAC) is characterized by a highly inflammatory microenvironment which contributes to its poor prognosis. Cancer-associated inflammation also promotes epithelial-to-mesenchymal transition (EMT) which contributes to the invasive and metastatic nature of the disease. Due to the inherent resistance of PDAC cells and drug resistance developed from gemcitabine (Gem) monotherapy, non-steroidal anti-inflammatory drug (NSAID), aspirin (Asp/A) has shown to increase the efficacy of Gem on pancreatic cancer cells. Metformin (met), a common anti-diabetic drug, has demonstrated a decrease in overall cancer mortality; however, some cell lines have developed resistance to treatment. Oseltamivir phosphate (OP) has been shown to reverse the phenotypic changes of EMT associated with chemoresistance and cancer progression by targeting neuraminidase-1 (Neu-1). Pancreatic cancer PANC-1 and Gem-resistant PANC-1 (PANC-1/GemR) cell lines were analyzed for cell viability via WST-1 assays upon treatment with each drug and drug combinations. Tumor tissue samples from immunocompromised mice that received no treatment, only Gem, or combined therapy with Asp/Met/OP/Gem were analyzed using immunohistochemistry for E- and N-cadherin to determine the presence of EMT. Sialidase assays were performed to elucidate mechanism of action for the various drugs in preventing cancer cell growth. A combination of Asp, Met, and OP work synergistically as chemotherapy-sensitizing agents in treating pancreatic cancer.

4. **ROLE OF PPARγ-DEPENDENT MICRORNA EXPRESSION DURING BREAST TUMOUR METASTASIS** Bradley J. Ross[1], Rachel E. Rubino[2] and Christopher J.B. Nicol[1-3]. Dept. of [1]Pathology & Molecular Medicine; [2]Division of Cancer Biology & Genetics, Cancer Research Institute; [3]Dept. of Biomedical & Molecular Sciences, Queen's University, Kingston, ON, Canada K7L 3N6.

Our lab previously showed peroxisome proliferator-activated receptor gamma (PPARγ) decreases environmental chemical carcinogen 7,12-dimethlybenz[a]anthracene (DMBA)-mediated breast tumour progression. My research will extend these findings by determining whether PPARγ exerts these anti-metastatic effects, in part, by altering microRNA (miR) signaling. I hypothesize that activation of PPAR$^{\gamma}$ upregulates anti-tumourigenic miRs that prevent breast tumour metastasis. To address this, I will use our established *in vitro* models to define the PPARγ miR expression changes that are altered during DMBA-mediated breast tumourigenesis. Human MDA-MB-231 breast cancer cells transfected with either lentiviral empty vector control (231^{EV}) or containing wildtype PPARγ ($231^{PPAR\gamma WT}$)expression plasmids were used for *in vitro* studies. Cells were pre-treated for 24 hr with vehicle or DMBA, +/- the PPAR ^{EV} activating drug rosiglitazone (ROSI). Treated cells were evaluated for metastatic changes using an invasion assay and by QRTPCR for gene expression changes. My data shows 231^{EV} cell invasion is significantly increased compared to $231^{PPAR\gamma WT}$ cells, and that increased DMBA-mediated invasion in both cells is significantly abrogated in the presence of co-treatment with ROSI. Expression analysis of 5 putative metastasis-related miRs were not significantly different between groups. My results suggest PPARγ expression and activation reduces the endogenous and DMBA-mediated invasion potential of human breast tumours. Global analysis of miRs altered under these conditions may provide clinically useful information as a novel way to treat breast cancer patients. Funding support: CBCF, Ontario Chapter (CJN).

5. **TUMOUR CELL DRUG RESISTANCE INDUCED BY THE PROGRAMMED DEATH LIGAND 1 (PD-L1) IMMUNE CHECKPOINT IS ASSOCIATED WITH AUTOPHAGY.** Sanwalka, D., Minassian L.M., Macdonald-Goodfellow S.K., Siemens, D.R. and Graham, C.H. Biomedical and Molecular Sciences

   The interaction between the Programmed Death Ligand 1 (PD-L1) immune checkpoint on the tumour cell surface with the Programmed Death-1 (PD-1) receptor on cytotoxic T lymphocytes (CTLs) leads to CTL inactivation, thereby promoting tumour cell escape from adaptive immunity. We previously demonstrated that signalling by PD-L1/PD-1 is bidirectional and leads to activation of oncogenic pathways as well as chemoresistance in tumour cells. We also have preliminary evidence that Immunity Related GTPase M, an important mediator of autophagy, is up-regulated by PD-1/PD-L1 reverse signalling. Autophagy is a well-established mechanism of chemoresistance in cancer cells. This led us to hypothesize that PD-1/PD-L1 signalling induces chemoresistance in tumour cells by up-regulating autophagy. The MEK/ERK signalling pathway is known to increase autophagy. Breast cancer cells exposed to recombinant PD-1 (rPD-1) showed a time dependent increase in ERK activation. Conversion of microtubule-associated protein light chain 3 (LC3)-I to LC3-II is a requirement for autophagosome formation and is a robust marker of autophagy. Exposure of human breast cancer cells to rPD-1 showed a time-dependent increase in LC3-II and in autophagosome formation. Treatment with rPD-1 also resulted in increased recruitment of LC3-II to the autophagic membrane. These results provide evidence that PD-1/PD-L1 reverse signalling activates autophagy as a potential mechanism of cancer cell chemoresistance. (Supported by a grant from the Canadian Institutes of Health Research).

6. **CLONAL HEMATOPOIESIS OF AGING IS ASSOCIATED WITH SPECIFIC IMMUNOLOGICAL PARAMETERS AND CLINICAL COMORBIDITIES: TOWARDS PRACTICAL SCREENING IN OLDER ADULTS.** Elina K. Cook[1], Terumi Izukawa[2], Dylan Johnson[1], Eva Bain[1], Jamie Hilland[1], Brooke Snetsinger[1], Bushra Momtaz[2], Janika Francis[3], Sherylan Young[3], Gili Rosen[2], Mina Jamali[3], Jonah Buckstein[1], Rena Buckstein[3] and Michael Rauh[1] [1]Department of Pathology and Molecular Medicine, Queen's University, Kingston, Canada [2]Baycrest Health Sciences, Toronto, Canada [3]Odette Cancer Centre, Sunnybrook Health Sciences, Toronto, Canada

   Introduction: In 2014 groups discovered that >10% of healthy people ≥65 years old show evidence of a potentially pre-cancerous population of myeloid peripheral blood cells; these originate from a mutant clone detectable by next-generation sequencing (NGS). This new condition is termed clonal hematopoiesis of indeterminate potential (CHIP), and carries an increased risk of developing blood cancers, cardio-metabolic events and death. The clone contains an acquired, distinguishing somatic gene mutation (e.g. in *TET2*, *DNMT3A*). It is unknown how CHIP emerges, however, *in vivo* models suggest that mutated clones alter and thrive in the host's inflammatory landscape. We hypothesize that persons with CHIP have an altered cytokine microenvironment compared to those without CHIP. Methods: We analyzed blood genomic DNA, serum and clinical data from 187 elderly participants (Baycrest, Sunnybrook). NGS of a hematological cancer-associated gene panel determined CHIP status. Cytokine levels were quantified by multiplex assays and evaluated using nonparametric statistics. Results: CHIP was detected in 27% of participants; the top mutated genes were epigenetic modifiers *TET2* and *DNMT3A*. CHIP patients had more comorbidities and differential monocyte and platelet counts. Stratifying CHIP into biologically meaningful groups (by genotype, clone size, mutation count) began to reveal unique aspects of inflammation.Conclusions: Uncovering the links between hematological mutant clones and inflammatory players will improve preventative medicine and targeted surveillance of hematological cancer progression in the elderly. (CCSRI Innovation Grant)

7. **ANTICANCER ACTIVITIES OF PPARγ IN HER2+ BREAST CANCER.** Lightbody Elizabeth D.[1], O'Connell Katie M.[2], Rubino Rachel E.[2], Apostoli Anthony J.[2], SenGupta Sandip K.[1], and Nicol Christopher JB.[1-3] [1]Departments of Pathology and Molecular Medicine; [2]Cancer Biology and Genetics, Cancer Research Institute; and [3]Biomedical and Molecular Sciences, Queen's University, Kingston, ON, Canada

HER2+ breast tumours are poorly differentiated, spread faster than HER2- tumours, and result in poor patient prognosis. Peroxisome proliferator-activated receptor (PPARγ)is a transcription factor with an emerging anti-tumourigenic role. Interestingly, PPARγ-activating drugs inhibit HER2 activation and decrease human breast cancer (BC) cell growth *in vitro*. Since the role of PPAR on HER2+ BC patient survival is unresolved, we generated a unique spontaneous *in vivo* breast tumour mouse model (PPARγ-NIC-KO), in which PPARγ deletion occurs within the same HER2+ transformed mammary epithelial cells that drive breast tumourigenesis. PPARγ-NIC-KOs have high mammary tumour incidences and multiplicity, and enhanced lung metastases compared to the parental strain. Protein analysis of PPARγ-NIC-KO tumours shows PPARγ loss is inversely correlated with increased HER2 phosphorylation at tyrosine 877 (pY877HER2) in tumourigenic tissue. Immunofluorescent analysis also showed HER2 H-scores was significantly highest among tumours from PPARγ-NIC-KOs but also correlated with targeted PPARγ loss in DMBA-induced primary and metastatic mammary tumours. A PPARγ-NIC-KO lung metastatic tumour cell line was created, known as PPARγ-NIC-KO^{lmet}. Migration, invasion and tumoursphere formation potential of PPARγ-NIC-KO^{lmet} and human BC cells was significantly decreased after treatment with a PPARγ activating drug (rosiglitazone). This is the first evidence that loss of PPARγ enhances HER2+ mammary tumour metastasis, and suggests PPARγ ligands may be useful novel therapeutics for HER2+ breast cancer patients. Funding Support: CBCF (CN) and Queen's Terry Fox-TTP (EL).

8. **THE ROLE OF STAT1 IN MODULATION OF THE TUMOUR IMMUNE MICROENVIRONMENT AND RESPONSE TO CHEMOTHERAPY IN HIGH-GRADE SEROUS OVARIAN CANCER.** Gillian Reid-Schachter, Nichole Peterson, Charles Graham, Runhan Ren, Peter Truesdell, Julie Francis, Andrew Craig, Madhuri Koti. Department of Biomedical and Molecular Sciences/Cancer Biology and Genetics Division/Queen's Cancer Research Institute/Queen's University, Department of Pathology and Molecular Medicine & Department of Obstetrics and Gynecology/Kingston General Hospital

High-grade serous ovarian cancer (HGSC) is the most prevalent and fatal histological subtype of ovarian cancer. One of the major problems with HGSC is that 70% of patients show resistance to chemotherapeutic drugs. It is now established that immune cells within the tumour microenvironment significantly contribute to tumor cell survival or apoptosis during chemotherapy. Previous work profiling inflammatory genes in HGSC tumours validated STAT1 expression and IFN induced genes as prognostic and predictive biomarkers in HGSC. RNA samples isolated from tumours of chemo-naïve HGSC patients obtained from the Ontario Tumour Bank were selected based on their clinical status as chemosensitive or resistant and their STAT1 expression. Total RNA isolated from the tumours was subjected to the PanCancer Immune Gene Profiling Panel from NanoString to profile the immune transcriptomic landscape. Gene expression analysis revealed significant differential expression of genes involved in cellular Type I interferon (IFN1) pathways between chemosensitive and resistant tumours. STAT1 silencing in ID8 cancer cells *in vitro* increased cell proliferation, migration, invasion and resistance to chemotherapy. Reduced STAT1 expression led to decreased CXCL10 production and differential chemokine expression *in vitro*. Ongoing *in vivo* studies aim to evaluate the mechanisms underlying variations in IFN pathways in HGSC. Cancer cell intrinsic IFN1 pathways, mediated by high expression of STAT1, potentially contribute to immune mediated chemotherapy sensitivity in HGSC. **Funding source**: Queen's

University Terry Fox Foundation Training Program in Transdisciplinary Cancer Research (Terry Fox Research Institute, TFRI), Cancer Research Society.

9. **INBUILT SUICIDAL MECHANISM AS A SAFETY CHECK FOR LONG TERM GENE THERAPY STUDIES.** Imtiaz Ahmad[1], Shalini Kot[1], [1]Evan Woodley, Meera Vyas[2], Karlaina Osmon[2], Sabrina Quazi[3], Zhilin Chan[4], Patrick Thompson[4] and Jagdeep S Walia[4] [1]Department of Biomedical and Molecular Sciences, [2]Centre for Neuroscience studies, [3]Department of biomedical computing and [4]Medical Genetics/Department of Pediatrics, Queen's University, Kingston, Ontario, Canada, K7L 2V7.

Background: Adeno-associated virus (AAV) is proving itself to be a powerful tool for gene therapy. However, recent studies have raised the concern regarding the safety of AAV due to reports of tumorigenesis. The use of suicide gene therapy (SGT) with heat inducible promoter of heat shock protein -70 (HSP-70), may address this concern by localized and controlled tumor killing. **Hypothesis and Objective:** The use of Herpes simplex virus thymidine kinase/gancyclovir (HSV-tk/GCV) SGT system under control of HSP-70 promoter will result in heat-inducible transcription of HSV-tk and apoptosis of only HSV-tk expressing cells in a localized and targeted manner. **Methods** included developing a dual promoter-transgene AAV viral construct, creating stably selected single cells clones, and analysis of expression and functionality of HSV-tk under various heat conditions and GCV concentrations.**Results:** Vector expressing GFP and HSV-tk was constructed and clones were generated. Western blot and PCR confirmed the expression of HSV-tk. The stably transfected clones showed significant killing/decreased survival at 41^0C under heat shock condition, as expected. However, a similar decrease in cell survival was also noted at 37^0C which indicated the promoter to be active at 37^0C; the etiology of this unexpected activation is now being investigated.

10. **GENETIC MODELING OF CALPAIN-1/2 AS THERAPEUTIC TARGETS IN BREAST CANCER.** James A. MacLeod, Yan Gao, Chris Hall, and Peter A. Greer. Department of Pathology & Molecular Medicine, Queen's University, Division of Cancer Biology and Genetics, Cancer Research Institute, Kingston, Ontario, Canada.

Calpains-1/2 are ubiquitously expressed intracellular Ca^{2+}-dependent proteases involved in a wide range of cellular processes, including migration, invasion, apoptosis and proliferation. Calpains cleave protein substrates involved in these processes; often in a manner that regulates, rather than abolishes, their functions. Calpain-1/2 isoforms are heterodimers consisting of an obligate common 28-kDa regulatory subunit encoded by *capns1*, and isoform specific catalytic subunits encoded by *capn1* and *capn2*, respectively. Clinical biomarker and genetic model studies support pro-tumorigenic roles for calpain-1/2 in breast cancer, including resistance to trastuzumab (Herceptin) and chemotherapeutics including doxorubicin and cisplatin. Orthotopic mouse engraftment of a conditional *capns1* knockout in a murine mammary carcinoma cell line revealed that *capns1* disruption abolished calpain-1/2 activity and was associated with loss of tumorigenesis *in vivo*. This was extended to the human MDA-MB-231 human basal breast cancer cell line; where RNAi knockdown and CRISPR/Cas9 knockout of *capns1* was is associated with attenuated tumor growth and metastasis in a mouse

xenograft model. Doxycycline-*capns1* inducible rescue in CRISPR knockout cells is being used to mimic a calpain inhibition treatment model. Collectively, our data argue that calpains-1/2 promote tumor growth and metastasis *in vivo*, and their inhibition will enhance the clinical efficacy of doxorubicin and other cancer therapies. This work was supported by the CIHR and CBCF.

11. EVALUATION OF DRUG RESISTANCE TRANSFER VIA EXTRACELLULAR VESICLES IN HUMAN OVARIAN CANCER CELLS. Jennifer F. Power & Susan P.C. Cole Pathology & Molecular Medicine

Ovarian cancer (OCa) has the highest mortality rate of all gynecologic malignancies. Symptoms of early-stage OCa are rarely detectable resulting in late-stage diagnoses and poor prognoses. First-line chemotherapy of OCa includes paclitaxel and carboplatin. Unfortunately, patients often relapse with drug-resistant disease, resulting in 5-year survival rates <45%. Extracellular vesicles (EVs) are nanosized membrane particles that facilitate cell-cell communication, and have been implicated in promoting drug resistance. Resistance can be conferred by multiple mechanisms including elevated levels of the ATP-binding cassette (ABC) transporters P-glycoprotein/ABCB1 (P-gp), MRP1/ABCC1, and/or ABCG2/BCRP. We aim to determine whether resistance may be transferred by EVs, initially using a matched pair of drug-sensitive and -resistant ovarian A2780 cell lines. Using a sulforhodamine B cytotoxicity assay, A2780-AD645 cells were confirmed to be 17-fold and >50-fold resistant to doxorubicin and paclitaxel, respectively, relative to parental A2780 cells after a 48 hr drug exposure. Furthermore, elevated P-gp levels were detected in whole cell and membrane-enriched extracts of A2780-AD645 cells by immunoblot, as expected. Finally, immunoblots of EVs isolated by differential centrifugation from conditioned media from cultured A2780 cells confirmed the presence of established EV markers CD63, CD81, and syntenin-1. Our results to date suggest the feasibility of using OCa cell lines to explore how EVs may mediate drug resistance. Future studies will determine if EVs from drug-resistant OCa cells can transfer resistance to sensitive OCa cells. Supported by CIHR MOP-133584 and the TFRI Transdisciplinary Training Program in Cancer Research.

12. A BREAST TUMOUR ANGIOGENIC ROLE FOR PPARγ SIGNALING. Jia Yue (Amelia) Shi[1], Anthony J. Apostoli[2], Rachel E. Rubino[3] and Christopher J.B. Nicol[1-31]Depts. of Biomedical & Molecular Sciences, Queen's University, Kingston, ON, Canada[2]Pathology & Molecular Medicine, Queen's University, Kingston, ON, Canada [3]Division of Cancer Biology & Genetics, Cancer Research Institute; Queen's University, Kingston, ON, Canada

Angiogenesis is crucial in breast tumour (BT) metastasis, the main cause of patient deaths. We showed that peroxisome proliferator-activated receptor (PPAR) γ signaling in mammary stromal endothelial cells (ECs) suppresses DMBA-mediated breast tumourigenesis *in vivo*. PPARγ activating drugs reportedly have anti-tumourigenic and anti-angiogenic effects, but the role of PPARγ signaling during BT angiogenesis is unknown. I hypothesized that EC loss of PPARγ increases angiogenic signaling during breast tumourigenesis. Serum was collected from (n=5/group) 8-12-week-old untreated mice, or (n=4/group) mice at necropsy post-treatment with DMBA (1mg/week p.o.) for 6 weeks and continued at week 7 on normal chow diet, or one supplemented with a PPARγ ligand (rosiglitazone, 4mg/kg/day) for 25 weeks. Expression changes were assessed using a Mouse Cytokine 23-plex serum assay kit. Serum expression of interleukins, chemotaxins and inflammatory

factors were significantly altered in PPARγ^{EC-KO} versus WTs ($p<0.05$). Aortic rings isolated from untreated WT and PPARγ^{EC-KO} mice were analyzed with VEGF±ROSI using a sprouting assay. Matrigel plugs with VEGF±ROSI, or conditioned media from human MDA-MB-231 breast cancer cells treated for 24hrs with vehicle or ROSI, were injected into mouse mammary fat pads (n=3 mice/group), and assessed for vascularity changes 7 days after implantation. ROSI co-treatment reduced EC sprouting and migration/invasion in WTs but not PPARγ-EC^{KO} aortae. These data are the first evidence that loss of EC-targeted PPARγ alters the angiogenic environment during breast tumourigenesis. Funding support: CBCF, Ontario Chapter (CJN), and CGS-M (JYAS).

13. **EVALUATING PROPHYLACTIC VACCINATION MODELS TO ASSESS TUMORIMMUNE CELL INTERACTIONS FOLLOWING TUMOR ENGRAFTMENT**. Kyle Seaver[2], Peter Greer[1] and Sam Basta[2]. [1]Division of Cancer Biology and Genetics, Cancer Research Institute, Department of Pathology and Molecular Medicine, Queen's University, Kingston, Ontario, Canada. [2]Department of Biomedical & Molecular Science Queen's University, Kingston, Ontario, Canada.

New avenues in cancer immunotherapies are investigating the use of prophylactic cancer vaccines, which are able to promote a robust anti-tumor immune response, ultimately resulting in tumor remission and increased survival in a variety of animal models. In general, tumor vaccines are often delivered therapeutically, demonstrating greatest efficacy when administered earlier during tumor development. In this study we have developed a prophylactic vaccine model consisting of dead tumor cells encompassing immune adjuvants. Employing this dead tumor call vaccine (DTCV) we demonstrate and increase survival of 37.5% at 60 days post tumor challenge compared to no vaccine. Furthermore, with the addition of adjuvants we were able to further increase the survival rate to 100% at 60 days post tumor challenge. With these models developed, we next want to elucidate how the use of a prophylactic vaccine impacts the immune environment and what role this plays in preventing tumor development and tumor eradication following tumor engraftment. Overall, this research will provide novel information into the tumor-immune interactions at play and contribute to the development of anti-cancer therapies that can be utilized to prevent tumor growth. (Terry Fox Foundation, Training program in Transdisciplinary Cancer Research).

14. **CO-EXPRESSION GENE NETWORKS ASSOCIATED WITH THERAPEUTIC RESPONSE IN OVARIAN CANCER** Jihoon Choi (presenter)[1] , Anastasiya Tarnouskaya[2] , Matt Nevile[1] , Margot Gunning[1] , Madhuri Koti[1] , Qingling Duan[1,2] [1]Department of Biomedical and Molecular Sciences, Queen's University, [2]School of Computing, Queen's University

Background: A major impediment in the management of ovarian cancer is that 50% of patients experience recurrent cancer following platinum-based chemotherapy. The aim of our study is to identify novel gene networks underlying variable response to platinum-based chemotherapy among ovarian cancer patients. **Methods:** We identified 287 patients diagnosed with ovarian serous cystadenocarcinoma from the Cancer Genome Atlas (TCGA): 197 sensitive and 90 resistant to platinum-based chemotherapy. Using transcriptomics data from this cohort, we clustered genes into co-expression modules based on similarity in expression values using a non-supervised machine learning algorithm (Weighted Gene Co-expression Analysis: WGCNA) in R. **Results:** We identified 13 co-expression modules correlated with platinum-based chemotherapy-response ($P<0.05$) in our ovarian cancer patients. Gene-set enrichment analysis and functional pathway prediction

analysis demonstrated that genes in co-expression modules share common biological and regulatory pathways. Analysis of over-represented transcription factor binding sites showed that genes in co-expression modules are co-regulated by common transcription factors. **Conclusions:** We demonstrated that groups of interconnected genes (co-expression networks), which are possibly co-regulated by common transcription factors, are correlated with platinum-based chemotherapy response in ovarian cancer patients. We will replicate our findings using similar datasets available from breast cancer patients from TCGA. Findings from our study could help facilitate genetic testing through identification of gene signatures to predict chemotherapy response as well as lead to novel drug targets given a better understanding of the biological mechanisms underlying chemotherapy response.

15. SENSITIZING DORMANT PANCREATIC AND BREAST CANCER STEM CELLS WITH INTERLEUKIN-6 AND HEPATOCYTE GROWTH FACTOR FOR TARGETED MULTIMODAL CHEMOTHERAPY. Manpreet Sambi*[1], William Harless[2], Myron R Szewczuk[1] [1]Department of Biomedical and Molecular Sciences, Queen's University, Kingston, Ontario, Canada [2]ENCYT Technologies, Inc., Membertou, Nova Scotia, Canada

Cancer stem cells (CSCs) are a small subset of cells found within tumor cells that are proposed to be the driving force behind cancer relapse. CSCs are known to be resistant to chemotherapy. However, CSCs can be activated to proliferate under the influence of inflammatory cytokines released by the host upon standard clinical treatment in response to injury requiring tissue remodeling. We hypothesize that chemotherapeutics in combination with oseltamivir phosphate (OP) and aspirin can block distinct repair pathways upregulated after treatment with chemotherapeutics and prevent chemoresistance. We tested the proliferative capacity of CSCs through exogenous exposure of human pancreatic PANC-1 and triple negative breast MDA-MB 231 cancer cell lines and their resistant variants to Interleukin-6 (IL-6) and Hepatocyte Growth Factor (HGF) treatment at concentrations to reflect serum levels following oncology surgical procedures. Cancer cells treated with HGF and IL6 for 12, 24, 48 and 72 hours followed by exposure to a a cocktail of paclitaxel, aspirin and OP for 72 hours. The cancer cell following treatment regimen was analyzed using the WST-1 assay. Preliminary data showed multimodal therapy to be more potent after initial exposure to cytokines when compared with cancer cells without pretreatment with cytokines as a control.

16. *PTEN* ASSOCIATED TYPE 1 INTERFERON RESPONSE IN PROSTATE CANCER CELLS. Natasha Vitkin, Abdi Ghaffari, Nichole Peterson, Robert Siemens, Madhuri Koti Department of Biomedical and Molecular Sciences/Cancer Biology and Genetics Division/Queen's Cancer Research Institute/Queen's University, Department of Urology & Department of Obstetrics and Gynecology/Kingston General Hospital

Prostate cancer (PCa) is the most commonly diagnosed cancer in Canadian men and can progress into an advanced form with poor prognosis. Loss of the tumour suppressor gene phosphate and tensin homolog (*PTEN*) is associated with advanced disease and early biochemical recurrence. Recent findings have shown that *PTEN* plays a role in regulating the cellular innate immune response by positively influencing Type I Interferon

(IFN1) pathways. The precise context and factors affecting the activation of IFN1 signalling by *PTEN* have not been characterized in PCa such that these can be therapeutically exploited. We examined the IFN1 response of human PCa cells with altered *PTEN* status by stimulating cells with IFN1 agonists including universal IFN1 (UIFN1), Poly I:C and Poly dA:dT. Activation of IFN1 stimulated genes was evaluated at gene and protein expression levels. Preliminary results indicated that cells with distinct *PTEN* statuses exhibit differential IFN1 responses. Given the role of IFN1 in modulation of the tumour immune microenvironment (TME) and disease prognosis, these findings are foundational towards understanding the role of cancer cells intrinsic *PTEN* loss and its contribution to altering the associated TME in PCa.

17. **SIALYLATION OF CELL SURFACE GLYCOPROTEINS FACILITATES FORMATION OF 3D MULTICELLULAR PROSTASPHERES BY ENHANCING CELL-CELL ADHESION, THEREBY PREVENTING DISSEMINATION OF METASTATIC CELLS.** Sabah Haq, Vanessa Samuel, and Myron Szewczuk. Department of Biomedical and Molecular Sciences, Queen's University, Kingston, Ontario, Canada.

Prostaspheres-based three dimensional culture models have provided insight into prostate cancer metastasis highlighting the importance of cell–cell interactions and the extracellular matrix in the tumor microenvironment. The cancer metastatic cascade is highly influenced by aberrant cell surface specific sialoglycan structures on glycoproteins. Prostasphere formation closely resembles the mechanism of cell-cell adhesion in the detachment stage of the metastatic cascade. Prostaspheres from human metastatic prostate carcinoma PC3 and DU145 cell lines and their respective gemcitabine resistant (GemR) variants were generated by using cyclic Arg-Gly-Asp-D-Phe-Lys peptide modified with 4-carboxybutyl-triphenylphosphonium bromide. Both DU145 and DU145GemR cells formed small prostaspheres. In contrast, PC3 and PC3GemR cells formed irregular multicellular aggregates at all concentrations of cyclo-RGDfK(TPP) peptide. DU145 cells expressed higher amounts of E-cadherin compared with PC3 cells. DU145 and PC3 cells and their drug resistant variants expressed different levels of α-2,3-SA and α-2,6-SA residues on the cell surface which correlated with the ability to form prostaspheres. Prostasphere volume was reduced following pretreatment with 2,6-SA-specific neuraminidase. These results suggest that the relative levels of specific sialoglycan structures on the cell surface glycoproteins correlates with the ability of prostate cancer cells to form prostaspheres and thus prevents the dissemination of metastatic cells.

18. **RET-MEDIATED INVASION IN THREE-DIMENSIONAL MICROENVIRONMENT MODELS.** Sarah m. Maritan, Eric Y. Lian, and Lois M. Mulligan Department of Pathology & Molecular Medicine; Queen’s Cancer Research Institute Division of Cancer Biology and Genetics, Queens's University, Kingston, ON.

The RET receptor tyrosine kinase plays critical roles during embryogenesis, where downstream signalling mediates cell migration, proliferation, and survival. However, oncogenic mutations or aberrant expression of

RET are linked to tumor spread in multiple tumors. Previous studies of RET-mediated invasion have used standard 2D culture methodologies, which may not reflect the in vivo microenvironment. Here, we developed an in vitro 3D model to characterize the signals critical to RET-mediated tumor spread. Using the SH-SY5Y neuroblastoma cell line that endogenously expresses RET, we assessed RET-mediated anchorage-independent growth and invasion into a surrounding collagen matrix. We have quantified the contributions of several downstream signalling pathways by individually blocking SRC, PI3K, FAK, STAT3, MEK, and integrinβ-1 signals, for their effects on RET-mediated invasion in 3D culture. We showed that inhibiting either PI3K or MEK decreases cell invasiveness, while inhibition of STAT3 had little effect. Further, integrinβ-1, FAK or SRC inhibition completely blocked invasion, consistent with an integrin-dependent mode of invasion in SH-SY5Y cells. Additionally, we showed that FAK and SRC signalling were critical for SH-SY5Y survival in 3D microenvironments. While several RET-mediated signalling pathways have been implicated in cell motility in 2D culture models, our findings suggest that specific signals may differ in their importance in a 3D microenvironment. These data provide further insight into the role of RET signalling in in vivo tumor spread. (Supported by the Cancer Research Society of Canada and the Canadian Institutes for Health Research (LMM), and by Ontario Graduate Scholarships and studentships from the Terry Fox Research Institute Training Program in Transdisciplinary Cancer Research (SMM, EYL), and by a Craig Jury Summer Studentship (SMM).)

19. **ROLE OF THE PROGRAMMED DEATH LIGAND 1 (PD-L1) IMMUNE CHECKPOINT IN THE ACQUISITION OF MALIGNANT PHENOTYPES IN TUMOUR CELLS.** Minassian L.M., Sanwalka D., MacDonald-Goodfellow S., Siemens, D.R. and Graham, C.H. Biomedical and Molecular Sciences

The interaction between Programmed Death Ligand 1 (PD-L1) on the tumour cell surface with the Programmed Death-1 (PD-1) receptor on cytotoxic T lymphocytes (CTLs) leads to CTL inactivation, thereby promoting tumour cell escape from adaptive immunity. Consequently, most studies have focused on elucidating how PD-1/PD-L1 affects the CTL phenotype leading to dysfunction. Our group obtained evidence that PD-L1/PD-1 signalling is bidirectional, so that this signalling axis leads to activation of oncogenic pathways as well as drug resistance in tumour cells. This led us to our hypothesis that reverse PD-1/PD-L1 signalling in tumour cells is a survival mechanism linked to increased metastasis and resistance to therapy. The MEK/ERK and PI3K/Akt oncogenic pathways are important for the development of malignant phenotypes. Breast cancer cells exposed to recombinant PD-1 (rPD-1) to stimulate PD-L1 reverse signalling showed a time dependent increase in ERK and Akt activation and no change in mTOR activation. In addition, breast cancer cells treated with rPD-1 were more invasive than cells treated with control media. To determine which signalling pathways are involved in PD-1/PD-L1 reverse signalling and identify potential druggable targets, breast cancer cells were treated with rPD-1 and RNA was collected for Nanostring™ analysis. PD-1 binding regulated gene expression in multiple signalling pathways. These results provide evidence that PD-1 binding to PD-L1 stimulates reverse signalling into tumour cells and increases their malignancy. (Supported by the Canadian Institutes of Health Research)

20. **EPIGENETIC, STRUCTURAL, AND FUNCTIONAL CHARACTERIZATION OF THE E2A-PBX1 ONCOGENIC TRANSCRIPTIONAL NETWORK**. Marina R. Lochhead, David N. Langelaan, Kyster Nanan, Steven P. Smith, David P. LeBrun Department of Biomedical and Molecular Sciences, Queen's University Division of Cancer Biology and Genetics, Cancer Research Institute, Queen's University

Acute lymphoblastic leukemia (ALL) is a cancerous hematological disorder originating in B-lymphoid progenitor cells. In 5% of ALL cases, the oncogenic transcription factor E2A-PBX1 is expressed as a result of the somatic chromosomal translocation 1;19. E2A-PBX1 comprises the three disordered N-terminal E2A transcriptional activation domains (AD) and the DNA-binding homeodomain of PBX1. These structural features suggest E2A-PBX1 recruits transcriptional co-activatiors by means of the activation domains and induces ALL through deregulation of PBX1 target genes. We have determined that the E2A AD1 interacts directly with the transcriptional co-activator CBP/p300 and that this interaction is required for leukemogenesis. In contrast to the current model of t(1;19)-induced ALL, we have found that E2A-PBX1 does not localize to PBX1 recognition sequences and instead localizes to genomic sites bound directly by the master B-lymphopoietic transcription factors, wt-E2A and EBF1. To this end, we have investigated the mechanism by which E2A-PBX1 associates physically with B-lymphopoietic enhancers. We have characterized interactions involving wt-E2A/EBF1 and E2A-PBX1 using sequential-ChIP and NMR spectroscopy. Additionally, we are looking at discerning which genes are deregulated by E2A-PBX1 and the mechanisms by which this happens using knockdown studies. Our results illustrate a revised model of the role of E2A-PBX1 in ALL suggesting the formation of a multi-protein complex at lymphopoietic enhancers comprising E2A-PBX1, wt-E2A/EBF1, and CBP/p300, which perturbs enhancer function and contributes to the development of ALL.
(Supported by CIHR and the Leukemia and Lymphoma Society)

Cardiac, Circulatory, and Respiratory Sciences

21. ALTERING ACTIVE VITAMIN D_3 SUPPLEMENTATION IN EXPERIMENTAL CKD, IRRESPECTIVE OF CHANGES TO CIRCULATING PTH, DO NOT MITIGATE THE DEVELOPMENT OF VASCULAR DISEASE. Svajger B[1]., Pruss C[1]., Laverty K[1]., Zelt .G.E[3]., Petkovich, M[1]., Holden R.M[2]., Adams M.A.A[1]. [1]Department of Biomedical and Molecular Sciences, Queen's University, Kingston, ON; [2]Department of Medicine Queen's University, Kingston, ON; [3]Department of Medicine, University of Ottawa, Ottawa, ON.

Body: Calcitriol is a primary treatment for secondary-hyperparathyroidism in CKD. Conflicting results exist about its use with some studies reporting survival improvement whereas others indicate increased incidence of vascular disease. This study examined the effects of altering the magnitude and frequency of calcitriol dosing in experimental CKD. Methods: CKD was induced in adult male Sprague-Dawley rats(n=42) using a high adenine diet. After 4weeks rats were stratified into calcitriol treatments: 0ng/kg (n=8), 5ng/kg QID(n=9), 20ng/kg SID(n=8), 20ng/kg QID(n=9), or 80ng/kg SID(n=8). Rats were sacrificed after 3weeks calcitriol treatment, with tissues harvested and blood collected. A control group(n=6) fed standard rat chow was included. Results: Both daily magnitudes (20ng/kg or 80ng/kg) reduced PTH relative to CKD after 1week ($p<0.05$). This large suppression effect was absent at 3weeks. All treatments elevated FGF-23 after 1 and 3weeks ($p<0.001$). Daily 80ng/kg had greater PTH suppression and FGF-23 elevation compared to 20ng/kg ($p<0.05$). PTH over-suppression was present in 15% of treated rats, yet 90% had calcified vessels and VWF was elevated in all groups ($p<0.05$). Altering dosing frequency did not markedly change any parameters. Conclusion: Only changing the magnitude of calcitriol dose significantly altered PTH and FGF-23, an effect lost over time. Although therapeutic PTH targets were attained no mitigation of vascular disease occurred in treated rats. These results indicate other treatment routes should be developed for hyperparathyroidism in CKD.

22. **FEMORAL PLAQUE QUANTIFICATION BY TWO-DIMENSIONAL ULTRASOUND FOR THE PREDICTION OF CORONARY ARTERY DISEASE**. Kayla Colledanchise, Laura Mantella, Marie-France Hétu, Milena Bullen, Julia Herr, Joseph Abunassar, Amer Johri. Department of Biomedical and Molecular Sciences. Queen's University, Kingston, Ontario Canada.

BACKGROUND: Femoral plaque, detected by vascular ultrasound, predates adverse cardiovascular events, such as myocardial infarction and cardiac death. However, the potential value of a femoral plaque screening tool is largely unexplored. **OBJECTIVE:** To determine the predictive value of a femoral plaque assessment for identifying significant coronary artery disease (CAD) in patients referred for coronary angiography. **METHODS:** Forty-five patients referred for coronary angiography underwent same-day femoral ultrasound scans. Mean intima-media thickness (IMT), maximal plaque height, and total plaque area were measured in various femoral territories of each patient. The extent of coronary artery luminal narrowing was determined by coronary angiography. Optimal cut-off values of IMT and plaque burden were determined using a receiver operating characteristic curve for identifying significant CAD. **RESULTS:** Common femoral maximal plaque height and total plaque area were the best predictors of CAD. Mean$\pm$SD maximal plaque height (3.07$\pm$1.62 mm versus 0.73$\pm$1.29 mm) and total plaque area (48.35$\pm$41.13 mm^2 versus 10.52$\pm$24.59 mm^2) were significantly higher in patients with CAD ($p \leq 0.0002$). Optimal threshold values of 1.7 mm for plaque height and 7.0 mm^2 for plaque area had an equal, high sensitivity of 91% and specificity of 78% for predicting CAD. **CONCLUSION:** Common femoral plaque burden is indicative of CAD. Femoral ultrasonography may serve as an accurate stratification tool in the integrated assessment of cardiovascular risk, reducing the usage of unnecessary, invasive downstream diagnostic procedures. (Supported by the Natural Sciences and Engineering Research Council of Canada, Heart and Stroke Foundation of Canada, Canada Foundation for Innovation, and the Ministry of Research, Innovation and Science).

23. **SENSORY-MECHANICAL RESPONSES TO HIGH-DOSE METHACHOLINE BRONCHOPROVOCATION IN HEALTHY NORMAL SUBJECTS.** Nilita Sood[1], Thomas Fisher[1], Taylar Wall[1], John T. Fisher[1], and M. Diane Lougheed[1]. [1]Department of Biomedical and Molecular Sciences, Queen's University, Kingston, ON.

Lougheed et al. (Lung 2012;190:17-22) have identified individuals who cough during high-dose methacholine but have normal airway sensitivity (COUGH). In COUGH, deep inspirations (DI) partially reverse small airway obstruction and dynamic hyperinflation, similar to classic asthma (CA) and cough variant asthma (CVA) (Turcotte et al. AJRCM 2011;183:A5541, Wasilewski et al. JAP 2016;120(9):1018-28). Understanding the clinical relevance of COUGH hinges upon characterizing the associated with DIs during high-dose methacholine in healthy individuals. Healthy individuals (18-65y) with no history of asthma, chronic cough or asymptomatic airway hyperresponsiveness attended 2 visits. Subjects performed baseline spirometry and body plethysmography, and were randomized to perform either: (i) traditional high-dose methacholine challenge using maximal-flow volume curves; or (ii) modified high-dose methacholine challenge using partial and maximal-flow volume curves and impulse oscillometry, at each dose to a maximum change (Δ) in FEV1 of 50% from baseline (MAX). Lung volumes, cough counts and breathlessness (Borg scale) at baseline and MAX were recorded, and compared using paired t-tests. 15 subjects (9 females; 31.4±7.3y) (Mean±SD) have been studied. Responses are summarized in Table 1. At MAX, subjects developed significant cough (3.5±4.7;p=0.0117) and bronchoconstriction (%ΔFEV1=-8.9±5.2%;p<0.0001), despite a preserved brochodilating effect (DIindex=1.37±1.24;p=0.0003). Future research comparing normal physiological responses to high-dose methacholine and DIs to individuals with CA, CVA and COUGH may elucidate the pathophysiologic differences between cough phenotypes. William M. Spear Endowment And Start Memorial Fund.

24. IN VIVO CHARACTERIZATION OF A TWO NOVEL MUSCARINIC RECEPTOR 3 (MR3) ANTAGONISTS: ABH 423 AND JHH 378. S. Vincent[1], K., Kobilka[2], H., Wess[4], J., Gmeiner[3], P. and Fisher[1], J.T. Department of Biomedical and Molecular Sciences, Queen's University[1], Kingston, Ontario, Canada; Department of Molecular and Cellular Physiology, Stanford University School of Medicine[2], Stanford, California, U.S.A; Molecular Signaling Section, Laboratory of Bioorganic Chemistry, National Institute of Diabetes and Digestive and Kidney Diseases[4], Bethesda, Maryland, U.S.A; and Department of Chemistry and Pharmacy, Friedrich Alexander University[3], Erlangen, Germany.

Anticholinergics are a first-line therapeutic approach for COPD and an emerging therapy in asthma (Wasilewski *et al.*, 2014). Current anticholinergic bronchodilators are non-selective muscarinic receptor (MR) antagonists that achieve selectivity via dissociation kinetics. We tested the *in vivo* efficacy and selectivity of two novel putative MR3 selective antagonists; ABH 423 and JHH 378. Experimental procedures met CCAC guidelines and were approved by Queen's University Animal Care Committee. Maximal respiratory resistance (Rrs) and minimum heart rate (HR) were measured in anaesthetized (sodium pentobarbital, 60 mg/kg) and mechanically ventilated adult, male, C57BL/6J mice. The log half maximal inhibitory concentrations (IC50) for 50 µg/kg Methacholine (MCh) challenge for ABH 423 and JHH 378 respectively were 1.496 e-9 and 1.489 e-10 Mol/kg for Rrs and 5.97 e-6 and 1.358 e-6 Mol/kg for HR. The log IC50s for Rrs and HR were significantly different from each other. We measured the effects of a single antagonist dose (1 e-07 Mol/kg) or saline on a cumulative MCh dose-response challenge (10 - 250 µg/kg). Both antagonists elicited a significant reduction in the bronchoconstriction response compared to saline with no significant effect on the HR response. Our data indicate that ABH 423 and JHH 378 act as highly selective MR3 antagonists *in vivo* with therapeutic potential. Supporting agencies: Queen's Spear Endowment for Pulmonary Research Queen's University[1], CIHR (MOP 81211)[1] and NIH-NIDDK[4]

25. PDE1C REGULATES THE DYNAMICS OF ACTIN-BASED STRUCTURES IN MIGRATING HUMAN ARTERIAL SMOOTH MUSCLE CELLS. Paulina Brzezinska[1], Darrin M. Payne[2], Jodi Mackeil[1], Jonah Burke Kleinmann[1], Donald H. Maurice[1]. Department of Biomedical & Molecular Sciences[1] and Department of Surgery[2], Queen's University, Kingston, ON, Canada.

Phenotypic remodeling and an associated increased migration of arterial smooth muscle cells (SMCs) are features of neo-intimal hyperplasia that promote occlusive vascular diseases, including post-angioplasty restenosis. The second messenger cAMP plays an important role in regulating cell migration, however its role in regulating the individual components involved in polarized cell migration, including the formation of actin-rich lamellipodial projections have been less characterized in arterial SMCs. Our study highlights the role of the cyclic nucleotide phosphodiesterase, PDE1C, in modulating this process as PDE1C activity and expression is induced in vascular proliferative disease. Visualization and quantification of lamellipodial projections was assessed in human internal thoracic artery smooth muscle cells (HITASMCs) by subjecting the cells to a modification of the transwell migration assay. Our findings show that siRNA-mediated knockdown or inhibition of PDE1C promotes lamellipodial protrusions in migrating HITASMCs. In contrast, we show that global increases in cAMP inhibit the formation of lamellipodial protrusions and reduce the ability of PDE1C knockdown, or its inhibition, to promote this event. These results contrast with the effects of PDE1C in mediating overall migration since PDE1C knockdown has a net inhibitory effect on migration. Consistent with this difference, perhaps being related to localized actions of PDE1C at the leading edge of migrating cells, we suggest that PDE1C may act locally, via a PKA/AKAP79-based signalosome to regulate lamellipodial extension. Supported by the Canadian Institutes for Health Research (CIHR).

26. VASCULAR IMAGING AS A BAROMETER FOR THE EARLY DETECTION OF CARDIOVASCULAR DISEASE (VIBE PROGRAM). Laura-Eve Mantella, Kayla Colledanchise, Tina Zhu, Joseph Abunassar, Amer Johri Department of Biomedical and Molecular Sciences, Queen's University, Kingston ON

Background: It is thought that many cardiovascular (CV) events are caused by vulnerable plaque. Such lesions are rupture-prone, in part due to neovascularization. We sought to examine whether carotid plaque neovascularization, detected by contrast-enhanced ultrasound (CEUS), is predictive of coronary artery disease (CAD) and CV events. **Methods:** CEUS was performed on patients undergoing angiography for the assessment of CAD. The neovascularization of each plaque was graded based on the presence and location of contrast microbubbles and then averaged to obtain the overall neovascularization value per patient. Gray-scale median (GSM) analysis was performed to quantify pixel intensity. **Results:** Preliminary data (n=32) showed that patients with significant CAD (stenosis ≥50%) had greater intraplaque neovascularization than non-CAD patients (1.49±0.63 vs. 0.24±0.26, $p<0.0001$). Furthermore, we found that plaque neovascularization was a better predictor of CAD (AUC=0.96) than total plaque area (AUC=0.83) or maximum plaque height (AUC=0.78). Upon GSM analysis, we found that neovascularized plaque had a higher proportion of pixels with intensity corresponding to that of fibrous tissue, compared to non-neovascularized plaque (8.86±6.62 vs. 2.11±1.87, $p<0.05$). Lastly, patients presenting with myocardial infarction showed greater plaque neovascularization than those with stable angina (1.38±0.72 vs. 0.70±0.76, $p<0.05$). **Conclusions:** Plaque neovascularization may serve as a predictor of significant CAD and future CV events. Further analysis is required to determine the value of carotid artery CEUS as a CV risk stratification tool. (Supported by the Heart and Stroke Foundation of Canada, Ministry of Research, Innovation and Sciences, Canada Foundation for Innovation, Canadian Cardiovascular Society and Bayer Inc.

27. VON WILLEBRAND FACTOR REGULATES DEEP VEIN THROMBOSIS IN A MOUSE MODEL OF DIET-INDUCED OBESITY. Alison Michels[1], Courtney N. Dwyer[1], Laura L. Swystun[1] and David Lillicrap[1] [1]Department of Pathology and Molecular Medicine, Queen's University

Obesity is associated with increased von Willebrand factor (VWF) and factor VIII (FVIII) levels and risk of deep vein thrombosis (DVT). We evaluated the role of VWF in DVT in a diet-induced obese (DIO) mouse model. DVT was induced by inferior vena cava (IVC) ligation in DIO mice and lean littermates. Thrombi were weighed and longitudinal sections were analyzed by IHC 24hr post-stenosis. DIO mice had increased VWF, FVIII, circulating granulocytes and erythrocytes after 2-weeks on a high-fat diet compared to controls. DIO mice had larger DVTs than controls (after 2&10-weeks on diets). DVTs from DIO mice contained more red thrombus that correlated with DVT size. High-intensity VWF staining co-localized with white thrombus (leukocytes/platelets) and low-intensity VWF staining with red thrombus. Quantitative IHC showed that DVTs from DIO mice had increased VWF and leukocytes but not fibrin/platelets. In DIO mice and controls, DVT size correlated with VWF, leukocytes, fibrin and platelets. VWF KO DIO mice were protected from developing DVT (55% decreased incidence) with DVT size decreased by 89%. Treatment of DIO mice with a polyclonal anti-VWF antibody decreased DVT incidence by 35% and size by 73%. DIO mice exhibit increased venous thrombogenicity that may be related to the role of VWF in platelet/leukocyte recruitment and FVIII binding. VWF is integral to DVT formation in this model and may be a novel therapeutic target.

Health Policy, Population Health, and Epidemiology

28. HEARING TESTING AND EAR TUBES IN ONTARIO - A CHANGING LANDSCAPE. Jason A. Beyea MD PhD FRCSC, Trina Stephens MSc, Emily Rosen MClSc, and Steve Hall MD MSc FRCSC. Department of Otolaryngology, Hotel Dieu Hospital, Queen's University, Kingston, Ontario, Canada.

Background: Tympanostomy tube insertion (TT) is the most common surgery performed on children in North America. Recent guidelines recommend hearing testing for all children who are candidates for TT. Rates of hearing tests before and after TT are unknown in Ontario. The aim of this study was to assess the usage of hearing tests in TT patients. Methods: Population-based, retrospective cohort study of patients ≤12 years of age who underwent at least one TT procedure between 1993-2014. Administrative health records from Ontario, housed at ICES, were used. The primary outcome was the percentage of patients who underwent a hearing test within 1 year before or after surgery. The secondary outcome evaluated geographic variation. Results: 300,752 patients underwent a TT procedure during this timeframe. From 1993 to 2014, pre-surgical hearing tests increased from 55.7% to 71.2% of patients, and post-surgical tests increased from 42.6% to 63.5%. However, the total number of hearing tests in patients undergoing TT decreased, reflecting more

stringent indications for performing TT surgery. Hearing testing ranged from 19.9% to 82.0% across LHINs. Conclusion: Although the percentage of pre- and post- surgical hearing tests is increasing in TT patients, the overall number of tests and population who undergoes TT is decreasing. This reflects ongoing refinement of the indications for surgical intervention in these children, and a more targeted use of these tests.

29. A POPULATION-BASED STUDY OF PATIENT AND SYSTEM FACTORS ASSOCIATED WITH ADVANCED CUTANEOUS MELANOMA IN ONTARIO. Mavor, M.E.[1,2], Richardson, H.[1,2,3], Miao, G.[1], Hanna, T.P.[1,4,5] 1.Division of Cancer Care and Epidemiology, Cancer Research Institute at Queen's University, 10 Stuart Street, 2nd Level, Kingston ON K7L3N6 Canada 2.Department of Public Health Sciences, Queen's University, Kingston ON K7L3N6 3.Canadian Cancer Trials Group, Cancer Research Institute at Queen's, 10 Stuart Street, Level 1, Kingston ON K7L3N6 4.Department of Oncology, Queen's University, 76 Stuart Street, Kingston ON K7L2V7 5.Institute for Clinical Evaluative Sciences at Queen's University, 21 Arch Street, Kingston ON K7L3L4

Objectives: We undertook a population-based study of melanoma in Ontario investigating the relationship between advanced melanoma and patient and health system factors. Methods: A 65% random sample of all invasive cutaneous melanoma in Ontario from 2007 to 2012 was identified in the Ontario Cancer Registry (OCR), and pathology reports on these cases were obtained, abstracted, and linked to OCR. Associations between advanced melanoma (thickness >2.0mm) and patient-, health system-, and tumor- factors were described. Multivariable modified Poisson regression was used to calculate relative risks and 95% confidence intervals. Effect modification by ulceration status was explored. Results: Of the 8620 people identified that had melanoma, 8043 had thickness information, 46.69% were female, and the median age at diagnosis was 62 years. In this cohort, 25.74% of patients had advanced melanoma. In multivariate analyses, advanced age (>85years vs. 55-65years; RR:1.53, 95% CI:1.37–1.71), male sex (RR:1.12, 95%CI:1.05-1.20), lowest SES quintile (RR:1.24 vs. highest quintile, 95%CI:1.12-1.38), and health region (RR range: 0.92–1.34, p=0.0052 for variable) were significantly associated with advanced melanoma. Presence of ulceration acted as an effect modifier. Conclusions: Disparate rates of advanced melanoma between the sexes, age, SES, and health region suggests there may be inequitable access to timely diagnosis of melanoma in Ontario. This highlights a potential opportunity for system improvement to ensure timely and equitable access to melanoma care.Funding: This studentship was funded by the Canadian Centre for Applied Research in Cancer Control (ARCC). ARCC receives core funding from the Canadian Cancer Society Research Institute (Grant #2105- 703549), Queen's University, Ontario Institute for Cancer Research, CIHR

30. ASSOCIATION BETWEEN THE UGT2B17 GENE DELETION AND WORSENED VASOMOTOR QUALITY OF LIFE IN POSTMENOPAUSAL WOMEN PARTICIPATING ON THE MAP.3 PREVENTION TRIAL. Braden Knight, Philip Lazarus, Thomas Massey and Harriet Richardson. Department of Public Health Sciences, Queen's University Kingston, Ontario, Canada

Background: Exemestane (EXE), an aromatase inhibitor, reduces the risk of breast cancer in postmenopausal women. However, participants have varied responses to this treatment in terms of efficacy and toxicity, possibly due to differences in EXE metabolism. One of the main elimination pathways for EXE is through glucuronidation by UGT2B17. **Aims:** This project examines the relationship between the *UGT2B17* gene deletion and menopause-related quality of life (QOL) in postmenopausal women. **Methods:** This study includes 3576 women nested within the CCTG MAP.3 trial, who were allocated to EXE or placebo treatment groups. Genotyping analysis was conducted with baseline blood cell DNA using real-time PCR and allelic

discrimination. Women heterozygous or homozygous null were considered "exposed". Women had the outcome if they experienced a ≥10% worsening in vasomotor QOL from baseline within the first year. A modified Poisson regression was used to calculate the relative risk. **Results:** There was no significant relationship between the *UGT2B17* deletion polymorphism and worsened vasomotor QOL (RR= 1.03, 95% CI: 0.92, 1.15). However, among only those women with no vasomotor symptoms at baseline but extremely bothersome symptoms at follow-up, the effect of the *UGT2B17* deletion polymorphism varied by treatment group (RR1= 1.09 and RR2= 0.21) respectively for EXE and Placebo. The *UGT2B17* deletion polymorphism could be used as a biomarker for extreme vasomotor QOL changes in breast cancer chemoprevention settings using exemestane. (Supported by the Terry Fox Foundation Training Program in Transdisciplinary Cancer Research, in partnership with CIHR)

31. THE ROLE OF OUTDOOR PLAY AND NATURE CONNECTEDNESS IN THE OCCURRENCE OF PSYCHOSOMATIC SYMPTOMS AMONG CANADIAN ADOLESCENTS. Caroline Piccininni and William Pickett. Department of Public Health Sciences, Queen's University, Kingston, Ontario, Canada.

This study explored how frequency of outdoor play and feelings of nature connectedness relate to the prevalence of psychosomatic symptoms, one indicator of poor mental health, among Canadian adolescents. An additional objective was to identify whether these associations differed by sex or age. A cross-sectional epidemiologic study design using data from the 2013/2014 cycle of the Health Behaviour in School-aged Children (HBSC) study was employed. The Canadian sample for this cycle included 30,153 students with an average age of 11 to 15 from 377 schools across the country. The association between outdoor play and psychosomatic symptoms differed by sex, but not by age group. Among female adolescents, spending greater than 0.5 hours/week outdoors was associated with a 24% reduction in the prevalence of high psychosomatic symptoms, compared to those who spent no time outdoors in the average week. Among male adolescents, no relationship between outdoor play and psychosomatic symptoms was observed. Self-perception of "connection to nature" as being important was associated with a 25% reduction in the prevalence of high psychosomatic symptoms. This association did not differ based on sex or age. This study highlights the potential importance of adolescent engagement with nature to promote their psychological well-being. It also emphasizes the importance of accounting for differences between the sexes when researching, planning, and implementing public mental health initiatives that make use of the outdoors. **Supporting Agency:** Canadian Institutes of Health Research (CIHR)

32. MORTALITY PATTERNS AMONG ONTARIANS WITH INTELLECTUAL AND DEVELOPMENTAL DISABILITIES Elizabeth Stankiewicz, Micheal McIsaac, Helene Ouellette-Kuntz, Department of Public Health Sciences Queen's University, Kingston, Ontario

This project will focus on patterns of mortality among adults with intellectual and developmental disabilities (IDD). The main patterns analyzed include mortality rates (overall by year as well as age and sex-specific), common causes of death, cause-specific mortality rates, and avoidable deaths. Additionally, this project will try to determine if the frailty index developed by Helene Ouellette-Kuntz and former students for persons with IDD is comparable to the Frailty Marker from Johns Hopkins. This study is part of an international effort to analyze and compare patterns of premature mortality among adults with IDD. Adults with IDD have lower life

expectancies than adults without IDD. Life expectancy has also been found to decrease significantly with increased level of disability. Supported by ICES Queen's

33. NEIGHBOURHOOD WALKABILITY AND OBJECTIVELY MEASURED ACTIVE TRANSPORTATION AMONG 10-13 YEAR OLDS. Gillian Williams; Dr. Ian Janssen, Department of Public Health Sciences

Background: Research suggests that the walkability of a neighbourhood's built environment can influence active transportation. Traditionally, measures of walkability and active transportation have been based on self-reported data collection and adult samples. The objective of this study was to examine the relationship between objectively measured neighbourhood walkability and active transportation among children. Methods: This was a cross-sectional study of 366 children (aged 10-13 years) from Kingston, Ontario. Participants wore a Garmin GPS watch to log their location during waking hours for 7 consecutive days. GPS data were analyzed in speciality software to identify how much time participants walked and cycled. A walkability index was created for each participant's home neighbourhood by combining several measures of how well streets connected to each other, proximity to destinations such as schools and parks, and safety features such 4-way-stop signs low traffic roads. Results: 9% of participants had no active transportation and the overall mean was 11.5 minutes/day (95% CI: 10.8, 21.1). Children living in neighbourhoods with the highest walkability quartile spent 17.1 minutes/day (95% CI: 15.6, 18.6) in active transportation compared to 6.7 minutes/day (95% CI: 6.0, 1.3) for children living in neighbourhoods in the lowest walkability quartile ($p<0.0001$).Conclusions: Children living in the most walkable neighbourhoods accumulated nearly three times more active transportation than those living in the least walkable neighbourhoods. **Supporting Agency**: The Heart and Stroke Foundation

34. INVESTIGATING CORTISOL PRODUCTION, PATTERN AND VARIABILITY AS MEDIATORS IN THE RELATIONSHIP BETWEEN SHIFT WORK AND METABOLIC SYNDROME Jennifer Ritonja[1], Kristan J. Aronson[1,2], Jill Korsiak[3], Andrew Day[4], Joan Tranmer[1,5] [1]Department of Public Health Sciences, Queen's University, Kingston, Canada [2]Divison of Cancer Care and Epidemiology, Cancer Research Institute, Queen's University, Kingston, Canada [3]Research Institute and Centre for Global Child Health, Peter Gilgan Centre for Research and Learning, The

Hospital for Sick Children, Toronto, Canada [4]Clinical Research Centre, Kingston General Hospital, Kingston, Canada [5]School of Nursing, Queen's University, Kingston, Canada

Shift work has emerged as a risk factor for many diseases, particularly cardiovascular disease (CVD). While the biological pathway by which shift work increases CVD risk is still not fully understood, it is hypothesized that disruption of cortisol during night work is an intermediate in this pathway. The main objective is to determine whether total cortisol production, diurnal pattern, or cortisol variability mediate the relationship between current shift work status and metabolic syndrome (MetS) among 326 female workers at Kingston General Hospital. Current shift work status was determined through intake interviews, and criteria for MetS was determined through clinical exams and lab tests. Urinary-free cortisol was measured over two 24-hour cycles, which included one night for shiftworkers. Diurnal cortisol production (AUC_G) and cortisol pattern (AUC_I) were calculated, as well as magnitude of variation for both. Shift work is associated with having metabolic syndrome (OR=2.41, 95% CI: 1.25-4.64) and with a higher metabolic syndrome score (β=0.45, 95% CI: 0.12-0.78) adjusting for confounders. Further, diurnal cortisol production is a mediator in the relationship between shift work and the metabolic syndrome score, but not with having metabolic syndrome. There was no evidence that AUC_I or either magnitude of variation are mediators. Our results provide evidence that diurnal cortisol production is a mechanism in which shift workers are at an increased risk for metabolic syndrome.

35. SHIFT WORK PATTERNS, CHRONOTYPE, AND OVARIAN CANCER RISK. Leung L[1,3], Grundy A[1,2], Aronson KJ[3,4], Koushik A[1,2] Université de Montréal Hospital Research Centre (CRCHUM), 850 Saint-Denis Street, 2nd Floor, Montreal, QC H2X 0A9, Canada, Department of Social and Preventative Medicine, Université de Montréal, Montreal, Quebec, Canada.Department of Public Health Sciences, Queen's University, Kingston ON K7L3N6 Division of Cancer Care and Epidemiology, Queen's Cancer Research Institute, Queen's University, Kingston, Ontario, Canada

Objectives: Circadian rhythm disruption is hypothesized to increase ovarian cancer risk. The association between shift work and epithelial ovarian cancer (EOC) risk was investigated. **Methods:** In a population-based case-control study conducted in Montreal, Canada (2011-2016), lifetime occupational histories with shift timing information were reported by 496 cases and 906 controls. Cumulative exposure to shift work (CSW) was assessed for each participant, and multivariable unconditional logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for the relationship between CSW tertiles and overall EOC risk. Multivariable polytomous logistic regression was used to estimate ORs for associations between CSW and EOC risk by tumour behaviour (invasive, borderline) and invasive cancer type (Type I, Type II). **Results:** 53.4% of cases and 51.7% of controls have ever worked shifts that included evenings and/or nights. There was no strong evidence for the association between CSW and overall EOC risk, and risk by tumour behaviour and invasive cancer type, where the OR for the highest CSW tertile vs. never working shifts was 1.20 (95%CI: 0.89-1.63) for overall EOC risk. Additional analysis on exposure to specific shift schedules indicated no EOC risk. **Conclusion:** Shift work causing circadian disruption is a "probable" carcinogen according to the International Agency for Research on Cancer, based mainly on breast cancer studies. In this investigation, shift work was not associated with EOC risk.

36. EXPLORING EXPECTATIONS OF PUBLIC STIGMA AS A MEDIATOR IN THE RELATIONSHIP BETWEEN OCCUPATIONAL PRESTIGE AND PROFESSIONAL MENTAL HEALTH CARE SEEKING IN THE GENERAL CANADIAN

POPULATION. Lyndsey A. Telega. Department of Public Health Sciences, Queen's University, Kingston, Ontario, Canada.

Occupational prestige has an important place in Canadian society where occupations are a point of hierarchal classification for individuals and families within the social structure. Occupational prestige, the subjective aspect of occupations, reflects a power differential inherent across various occupations, which can lead to differential access to health resources. It is has been well researched that mental health-related stigma has a small to moderate detrimental impact on help-seeking for a mental illness, therefore, partial mediation by expectations of public stigma, signified by a reduction in the strength of the path from occupational prestige to mental health care seeking, was hypothesized. A secondary analysis of the 2010 Canadian Community Health Survey and rapid response stigma modules was conducted. A multivariate linear regression analysis was used to explore the mediating relationship between occupational prestige and expectations of public stigma (path a). Logistic regression analyses were used to explore the mediating relationship between expectations of public stigma and professional mental health care seeking (path b), and the direct relationship between occupational prestige and professional mental health care seeking (path c). Neither the indirect effect (path a × b) nor the direct effect (path c) were significant, meaning that the relationship is classified as no effect non-mediation. Expectations of public stigma is not a mediator and there is no relationship between occupational prestige and mental health care seeking. (Supported by the BP Singh Mental Health Fellowship Award and the Department of Public Health Sciences).

37. LIFETIME CAFFEINE INTAKE AND THE RISK OF EPITHELIAL OVARIAN CANCER. Simran K. Sandhu, Anne Grundy, Kristan J. Aronson, & Anita Koushik. Department of Public Health Sciences, Queen's University, Kingston, Ontario, Canada.

Purpose: To examine the association between caffeine intake and risk of epithelial ovarian cancer (EOC) overall, by tumour behaviour (invasive vs. borderline), and invasive cancer type (Type I vs. Type II). *Methods:* Analyses were conducted on 497 cases and 904 controls from the PRevention of OVArian Cancer in Quebec (PROVAQ) study, a population-based ovarian cancer case-control study in Montreal (2011-2016). Data collection included asking women about their lifetime consumption of caffeinated beverages and exposure was represented by average caffeine intake over the lifetime. Multivariable unconditional logistic regression was used to estimate odds ratios (ORs) with 95% confidence intervals (CIs) for the association between quartiles of caffeine intake (based on the distribution among controls) and risk of EOC. Multivariable polytomous logistic regression was used to estimate associations of caffeine intake with specific tumour behaviours and invasive types. *Results:* The OR (95% CI) for the highest versus lowest quartile of caffeine intake was 1.21 (0.85-1.70; p_{trend}=0.3) for overall EOC, 1.32 (0.90-1.93; p_{trend}=0.1) for invasive EOC, and 0.99 (0.54-1.80; p_{trend}=0.8) for borderline EOC. There were no appreciable differences in ORs for invasive Type I and Type II tumours. *Conclusions:* These findings do not strongly support an association between caffeine intake and EOC risk.

38. ASSOCIATION BETWEEN TUMOR SIZE AND SURVIVAL IN PATIENTS WITH SURGICALLY RESECTED INTRAHEPATIC CHOLANGIOCARCINOMA IN ONTARIO. Suriya J. Aktar, Harriet Richardson, Jina Zhang-Salomons, Sulaiman *Nanji,* Christopher M. *Booth,* and Jennifer A. Flemming. Cancer Care & Epidemiology, Queen's Cancer Research Institute, Queen's University, Kingston, Ontario, Canada.

Background/Aims: Intrahepatic cholangiocarcinoma (IHCC) is a rare but deadly primary liver cancer. Controversy exists regarding the association between tumor size and overall survival (OS) in IHCC. We aimed to examine this relationship in surgically resected patients with IHCC in Ontario. Methods: This is a retrospective population-based cohort study of surgically resected patients diagnosed with IHCC between 2002 and 2012 using the Ontario Cancer Registry and pathology from Cancer Care Ontario. The primary exposure variable was size of the largest tumor and the primary outcome was 5-year OS. The association between tumor size and OS was assessed using Cox proportional hazard regression after adjusting for confounders. Results: A total of 121 cases were identified, median age 63.9 (IQR: 30.7-86.0), 43% male, median tumor size 6 cm (IQR: 0.6-13.0) and median follow-up time 37.6 months (IQR: 0.3-126.6). After multivariate Cox analysis, there was no association between tumor size and OS (HR=0.99, 95% CI: 0.88-1.10, P = 0.79). Factors that were associated with worse OS were male sex (HR= 2.47, 95% CI:1.30-4.71, P = 0.005) and higher tumor number (HR=1.82, 95% CI: 0.93-3.55, P = 0.08). Conclusion: In this population based study of surgically resected patients with IHCC, there was no association between largest tumor size and OS. Supporting agency: New Clinician Scientist Award, SEAMO.

39. HIGH LEVELS OF SOCIAL AND PHYSICAL INVOLVEMENT IN TEAM SPORT ARE ASSOCIATED WITH ADOLESCENT SUBSTANCE USE BEHAVIORS. Dylan O'Sullivan, Randy Boyes, Brooke Linden Department of Public Health Sciences

Team sport participation during adolescence is associated with physical and social benefits, but recent evidence suggests sport participation may also be related to increased risk behavior. Using the 2013-14 Canadian Health Behavior in School Aged Children (HBSC) we examined the relationship between sport participation and substance use. Our analysis resulted in three important findings: (1) the effect of engagement in team sports depended on which substance was examined; (2) the strength and direction of these relationships varied by gender, with team sport participation associated with increased binge drinking and use of smokeless tobacco in both boys and girls, but lower prevalence levels of cannabis use, smoking, and use of hard drugs in girls alone; (3) The type of sport engagement, both social (sports team as primary peer group) and physical (higher number of days/week physically active), that were most associated with substance use also varies by gender. For males, the combination of physical and social involvement conferred the highest risk, while social involvement alone conferred the greatest risk for females. While team sport participation confers only a small increased risk for substance use, the prevalence of sport participation results in a large population impact. Given the impact of team sport participation on adolescent substance use, interventions such as policies encouraging adolescents to engage in a variety of extracurricular activities beyond team sports should be explored.

Inflammation, Infection and Immunity

40. $\gamma\delta$ T **CELL CONTROL OF INFLAMMATORY PAIN.** Jelena Petrovic[1], Jaqueline Silva[1,2] and Nader Ghasemlou[1,2] Department of [1]Biomedical and Molecular Sciences and [2]Anesthesiology and Perioperative Medicine, Queen's University, Kingston, ON, Canada

Inflammatory pain is a result of the body's biological response to inflammation induced by foreign or harmful stimuli such as pathogen (e.g., bacterial) invasion or tissue injury (e.g., post-surgical wound). It has been demonstrated that immune cells will enter the site of infection/injury and secrete mediators, which can act on nociceptors to transduce pain signals to the peripheral and central nervous systems. However, the underlying mechanisms surrounding those immune cell(s) mediating the sensitization of nociceptors (causing hypersensitivity) during inflammation remains unresolved. $\gamma\delta$ T cells found in epithelial tissue near nociceptive sensory nerve fibres play a role in wounding healing and inflammation, but their contribution to pain remains unknown. Using mice lacking $\gamma\delta$ T cells (TCR$\delta^{-/-}$) and wild-type littermate controls (TCR$\delta^{+/+}$), behavioural hypersensitivity responses were assessed using models of inflammatory pain. Behavioural hypersensitivity responses were characterized using mechanical (von Frey test) and thermal (Hargreaves radiant heat/acetone cold test) assays to assess differences in baseline and post-injury responses. Our findings suggest an important role for these cells in the control of nociceptive outcomes in both naïve and injured animals. Ultimately, the role that $\gamma\delta$ T cells play in inflammatory pain could provide novel cell-specific drug targets that may provide safe and more effective treatment for acute pain.

41. INVESTIGATING THE EFFECTS OF IL-27 ON ENDOSOMAL TOLL-LIKE RECEPTOR EXPRESSION AND ACTIVATION IN HUMAN MONOCYTES AND MACROPHAGES. Natalya Odoardi[1], Carlene Petes[1], Katrina Gee[1]. [1]Department of Biomedical and Molecular Sciences, Queen's University, Kingston, ON.

Interleukin(IL)-27 is a heterodimeric cytokine composed of two subunits which has both pro- and anti-inflammatory functions. We have previously shown that IL-27 enhances Toll-like receptor (TLR)-4 expression and function on human monocytic cells. In general, TLRs are important innate immune sensors that recognize pathogenic molecular patterns such as viral and bacterial products. When activated, these receptors induce a signaling cascade to initiate the production of pro-inflammatory cytokines to mount an immune response against invading pathogens. Specifically, TLR 7/8 and 3 are found within the endosome of various immune cells and recognize ssRNA and dsRNA, respectively. RNA viruses such as influenza A virus (IAV) or HIV induce both TLR7/8 and TLR3 responses. Previous studies have reported that IL-27 inhibits HIV and IAV viral replication. To investigate whether IL-27 modulates innate immunity to such viral infections, we measured the effects of IL-27 on endosomal TLR expression and responsiveness. Flow cytometry analysis of TLR3 and TLR7 expression revealed that IL-27 treatment specifically upregulated both intra- and extracellular levels of TLR7, but not that of TLR3, in both monocytes and macrophages. Analysis of secreted pro-inflammatory cytokines demonstrated that pre-treatment with IL-27 increased pro-inflammatory cytokine production in response to TLR7 ligation.

This investigation suggests that IL-27 has specific modulatory effects on TLR7 by enhancing expression and pro-inflammatory cytokine production in both human monocytes and macrophages.

42. NASAL AND PERIPHERAL BLOOD GROUP 2 INNATE LYMPHOID CELL (ILC2) LEVELS IN RESPONSE TO NASAL ALLERGEN CHALLENGE IN PARTICIPANTS WITH ALLERGIC RHINITIS. Mark W. Tenn[1], Jenny Thiele[1,2], Anne K. Ellis[1,2,3] [1] Department of Biomedical and Molecular Sciences, Queen's University, Kingston, Ontario, Canada [2] Allergy Research Unit, Kingston General Hospital, Kingston, Ontario, Canada [3] Division of Allergy & Immunology, Department of Medicine, Queen's University, Kingston, Ontario, Canada

Background Peripheral group 2 innate lymphoid cells (ILC2s) produce IL-5 and IL-13, drive Th2 inflammation, and are increased in individuals with allergic rhinitis (AR) following a nasal allergen challenge (NAC). However, the identification of ILC2s in nasal samples has been sparsely explored. In participants with birch pollen-induced AR, we quantified the frequency of both nasal and peripheral ILC2s before and after NAC. **Methods** 11 birch-allergic and 8 non-allergic individuals were recruited and underwent a NAC with birch pollen extract. Nasal lavage (NL) and peripheral blood mononuclear cells (PBMCs, isolated from peripheral blood) were collected at baseline and 4 hours post-challenge. All samples were stained with fixable viability dye (PBMCs only), lineage (Lin) surface markers, CD45, CRTH2, and CD127 antibodies. Stained cells were acquired using a Beckman Coulter FC500 and a FACSAria III cell sorter. GraphPad Prism 6 was used for statistical analysis. **Results** A trend was observed suggesting an increase in the frequency of both nasal ILC2s (defined as Lin-CD45+CRTH2+CD127+, p=0.08) and nasal non-ILC2s (defined as Lin-CD45+CRTH2-CD127+, p=0.06) in birch-allergic participants following a NAC. This trend was absent for both cell subsets in peripheral blood. **Conclusions** In NL samples, we demonstrated a trend suggesting an increase in both nasal ILC2s and nasal non-ILC2s after allergen challenge. This suggests that ILC2s may play a role locally in the nose in individuals with AR.

43. IL-30-INDUCED PROINFLAMMATORY CYTOKINE EXPRESSION IS DEPENDENT ON ENGAGEMENT OF THE WSX-1 RECEPTOR IN HUMAN IMMUNE CELLS. Carlene Petes[1], Mélissa Mariani[2], Yawen Yang[1], Nathalie Grandvaux[2], Katrina Gee[1] [1] Department of Biomedical and Molecular Sciences, Queen's University, Kingston ON, Canada, K7L3N6; [2] Department de biochimie et médicine moléculaire, Université de Montréal, Centre de Recherche du CHUM (CRCHUM), Montréal PQ, Canada, H2X 0A9

IL-30 is a newly described cytokine and belongs to the IL-12 family, which are well described to modulate CD4 T cell development. IL-30 is the IL-27 p28 subunit in the absence of binding to EBI3. Since IL-30 and IL-27 share a subunit, it is speculated that IL-30 may share receptor usage with IL-27. Indeed, both cytokines interact with the WSX-1 and gp130 receptor chains, though the requirement for these receptors in terms of IL-30 function has not been defined. Little is understood regarding the activities of IL-30 in human immune cells. Thought to function as an inhibitor of gp130 receptor signaling, IL-30 has been documented to modulate inflammatory

responses in murine cells. Thus, we investigated the receptor requirements and potential inflammatory role for IL-30 in human CD4 T cells and monocytes. We demonstrate that similar to IL-27, IL-30 enhances IFN-γ expression while inhibiting that of IL-17 in cultured human CD4 T cells. Furthermore, in human monocytes, IL-30 induces the proinflammatory chemokine IP-10 and upregulates TLR4 expression to prime cells for enhanced LPS-induced TNF-α production. We found that optimal IL-30-mediated signaling required WSX-1, compared to that of IL-27, which relied on both WSX-1 and gp130. Taken together, we attribute novel roles for IL-30 in promoting Th1 cytokine expression as well as the release of proinflammatory cytokines from primary human monocytes in a WSX-1-dependent manner. *Research funded by a grant from Natural Sciences and Engineering Research Council of Canada (NSERC). CP is funded by NSERC PGS-D.*

44. CELLULAR AND MOLECULAR MECHANISMS INVOLVED IN INFLAMMATORY PAIN. Jaqueline Silva, Jelena Petrovic, Ian Gilron, Nader Ghasemlou Department of Biomedical and Molecular Sciences

Tissue injury results in an inflammatory response where immune cells are recruited, with pain generation: molecular and cellular interactions between the nervous and immune system are crucial to this process. We characterized the contribution of monocytes that mediate hypersensitivity, which are responsible for a high expression of CCL17 and CCL22. Thus, the aim of this study was to evaluate the role of both chemokines in the generation of pain. Mice received an intraplantar injection of CCL17 (30 and 300 nM), CCL22 (30 and 300 nM), a combination of both (30nM) or saline, and behavioral analysis was performed at 1, 3, 6, 24, 48 and 72 hours post injection. Mice presented mechanical and cold hypersensitivity at 1 and 3 hours post injection with all treatments, but did not show heat hypersensitivity. Also, the combination of CCL17 and CCL22 resulted in higher scores of mechanical hypersensitivity. CCL17 and 22 acts through binding to CCR4 receptor, so next we evaluated its role in pain. To do this, we injected mice with CCR4 antagonist (2 and 10mM) combined with CCL22 (30nM) and evaluated pain response at 1, 3 and 6 hours post treatment. Pain behavior in both groups was drastically reduced, suggesting that these chemokines elicits pain through CCR4 activation. So far, we conclude that CCL17 and 22 are important for pain behavior and acts through CCR4 receptor.

Neuroscience Research

45. A MULTI-MODAL IMAGING APPROACH TO ASSESS THE RELATIONSHIP BETWEEN STRUCTURAL AND PHYSIOLOGICAL CHANGES FOLLOWING SPORT CONCUSSION. Allen A. Champagne, BSc, BA, Nicole S. Coverdale, PhD, Stephen H. Scott, PhD, Clarisse I. Mark, PhD, Douglas J. Cook, MD, PhD. Centre for Neuroscience Studies, Queen's University, Kingston, Ontario, Canada.

The purpose of this study was to examine the relationship between structural white matter (WM) changes after sport-related concussion, and cerebrovascular reactivity (CVR). Eight concussed athletes (20±1 years) at 12±4 days post-injury completed a sensorimotor battery (KINARM Standard Tests^{TM}), followed by neuroimaging. Thirteen age-matched athletes (20±2 years) with no history of concussion were included as controls. The imaging protocol included diffusion tensor imaging (DTI), and a dual-echo pseudo-continuous arterial spin labeling sequence with a boxcar hypercapnic breathing challenge to assess WM and grey matter (GM) CVR. Although the groups did not differ in cognitive, motor or sensory functions, compatible with recovery, significant structural differences (increased fractional anisotropy (FA) and decreased radial diffusivity (RD)) were characterized in the Injured group using Tract-Based Spatial Statistics (TBSS). The significant intersecting FA and RD voxels were used as a seed for probabilistic tractography, which subsequently guided the regional analysis of GM vascular reactivity. Despite a strong relationship between FA and RD (r^2=0.91; *P*=0.000), nonparametric correlations showed no significant associations between FA (r^2=0.012; *P*=0.63) or RD (r^2=0.006; *P*=0.75) and co-localized WM CVR. Furthermore, no group difference in regional GM CVR was found in the cortical target (Control=0.24±0.16 %BOLD/mmHg; Injured=0.21±0.31 %BOLD/mmHg; *P*=0.86). Our findings suggest a discrepancy between rates of clinical recovery and dynamic changes in the WM, which may play a role in the neurodegenerative processes associated with repeated concussions. Funding This work was supported by the Canadian Institutes of Health Research (CIHR) and the Natural Sciences and Engineering Research Council (NSERC) through a Collaborative Health Research Project Grant (#315705; PI IS Johnsrude).

46. THE PADS STUDY: PROBIOTICS ALLEVIATING DEPRESSIVE SYMPTOMS. Caroline Wallace[1], Jane Foster[2,3], Sidney H. Kennedy[3], & Roumen Milev[1,4] [1]Centre for Neuroscience Studies, Queen's University; [2]Department of Psychiatry and Behavioural Neurosciences, McMaster University; [3]University Health Network; [4]Department of Psychiatry, Queen's University.

Preclinical and clinical studies have shown that consuming probiotics can improve mood, anxiety, and cognition, and alter brain activity. Data from our recent open-label, 8-week pilot study provided the first evidence of these effects in depressed patients, with significant improvements observed in mood, anhedonia,

and sleep quality. To further support this evidence and expand upon the search for biomarkers in depression, data from this pilot study is being used to plan a 16-week, double-blind randomized placebo-controlled trial. Participants diagnosed with depression recruited from the Kingston area will orally consume a probiotic supplement containing *Lactobacillus helveticus* and *Bifidobacterium longum* (Probio'Stick®, Lallemand Health Solutions) or placebo once daily. At week 8, participants will be assessed for responsiveness; non-responders will receive an increase in dose and responders will remain on the initial dose. Clinical data will be collected using a battery of validated scales assessing mood, anxiety, cognition, sleep, and diet; sleep will also be assessed objectively with an ambulatory polysomnogram. Neuroimaging data will be collected using magnetic resonance imaging and electroencephalography to look at functional, structural, and electrical changes in the brain; molecular data will be collected from blood, stool, and urine samples to look at levels of cytokines and serotonin, and explore potential genes and proteins that may predict outcomes in depression. We expect results to replicate and expand on our pilot data, demonstrating that probiotics are effective in alleviating symptoms of depression. An informatics-based approach will be used to integrate clinical, neuroimaging, and molecular data to look for biomarkers that indicate disease state and predict antidepressant-like response to the probiotic. (Supported by Lallemand Health Solutions and Ontario Brain Institute)

47. CHARACTERIZATION OF THE INFLUENCE OF CIRCADIAN RHYTHMS ON SOMATOSENSATION. Kaitlyn Tresidder, Julia Segal, Ian Gilron, Nader Ghasemlou. Centre for Neuroscience Studies, Department of Biomedical and Molecular Sciences, and Department of Anesthesiology, Queen's University, Kingston, ON, Canada

Somatosensory modalities include mechanoreception (touch), thermoreception (hot/cold), and nociception (pain). Sensory stimuli are transmitted through specific ion channels and receptors that can be activated and/or sensitized by various factors. Many of these channels have also been implicated in pain conditions, including neuropathic and inflammatory pain. Our research group has shown that patients with chronic neuropathic pain often exhibit circadian fluctuations in pain intensity, reporting significantly higher pain levels in the evening than during the day. We therefore sought to understand whether a link exists between circadian rhythms and somatosensory activity. To this end, we used standard and newer behavioural assays to measure mechanical, thermal and cold sensitivity in C57BL/6 mice. Surprisingly, we found a circadian effect only in the thermal sensitivity of naïve males, with mice displaying a higher sensitivity at 9am than at 9pm. Pharmacological characterization of this effect by intraplantar injection of capsaicin suggests that the observed rhythm is modulated by the transient receptor potential vanilloid 1 (TRPV1) ion channel, as mice displayed a higher level of sensitivity when injected at 9am than at 9pm. Additional data to be shown at the time of presentation will provide a more complete characterization of this circadian pattern and the mechanisms through which these effects are controlled are being further examined. Our work will lead to an increased understanding of the underlying physiology of ion channels and their link to hypersensitivity.

48. IMMUNOHISTOCHEMICAL CHARACTERIZATION OF SENSORY NEURONS SURROUNDED BY POSTGANGLIONIC SYMPATHETIC BASKETS IN THE MOUSE TRIGEMINAL GANGLIA. Hanin Alsaadi (Ph.D. Candidate), Nader Ghasemlou and Michael D. Kawaja Centre for Neuroscience Studies, Queen's University, Kingston, Ontario

Following peripheral nerve injury, postganglionic sympathetic axons sprout into affected sensory ganglia and form perineuronal plexuses around specific primary sensory neurons. These basket-like structures have been shown to play an important role in the development and maintenance of chronic pain. In this study, we sought to determine the phenotype of the trigeminal ganglia neurons surrounded by postganglionic sympathetic plexuses. Here we utilized mice that express nerve growth factor (NGF) under the control of glial fibrillary acidic protein promoter, as these mice display the spontaneous formation of sympathetic baskets in sensory ganglia (i.e., in the absence of nerve injury). Preliminary immunostaining results show that the vast majority of those sensory neuronal cell bodies surrounded by sympathetic plexuses in the trigeminal ganglia are immunopositive for 1) the NGF receptor trkA, 2) a second NGF receptor p75, and 3) calcitonin gene-related peptide. These same sensory neurons with sympathetic basket lack immunostaining for the isolectin B4, substance P, TRPV1, and aquaporin. These results reveal that the nociceptive sensory neurons surrounded by sympathetic plexuses are NGF-sensitive, peptidergic, and heat insensitive. This study begins to shed light on the mechanisms that provide specificity in the formation of sympathetic plexuses following peripheral nerve injury. This knowledge is imperative for developing targeted interventions for chronic pain conditions. This work is funded by Queen's University School of Medicine to (MK), and King Saud bin Abdulaziz University for Health Sciences Scholarship to (HA).

49. OLFACTORY FUNCTIONING IN DEPRESSION AND THE EFFECTS OF TRANSCRANIAL MAGNETIC STIMULATION. Hannah C. Taalman,[1]., Roumen Milev.[2] [1] Centre for Neuroscience Studies, Queen's University, Kingston, ON [2] Department of Psychiatry, Queen's University, Kingston, ON

Research examining olfactory functioning in depressed individuals has indicated a reciprocal relationship between the two, with depression negatively impacting olfaction. Extensions of this research have demonstrated olfactory function improvement after successful pharmaceutical treatment. It is, however, unknown if transcranial magnetic stimulation (TMS) has a similar effect. Our objective is to determine if individuals receiving TMS for depression exhibit improved olfactory functioning when there is baseline olfactory dysfunction. We hypothesize that depressed individuals will have poorer olfactory functioning compared to controls before treatment, but little to no difference after. We recruited twenty depressed individuals receiving TMS at Providence Care Hospital, as well as ten healthy controls from the Kingston community. The olfactory function of participants was tested before and 7-14 days after treatment using Sniffin' Sticks Expanded Test (examining olfactory threshold, discrimination, and identification). Depression severity was also measured using a number of scales. Preliminary results identified a significant difference in olfactory discrimination of depressed before TMS compared to after treatment. The preliminary analysis demonstrated a significant difference in depression scores between depressed and controls both before and after treatment. Depressed and controls differed only in discrimination after treatment, where depressed performed significantly better than controls. We conclude that while there is no difference between the olfactory functioning of depressed and controls at baseline, TMS improves the discrimination ability of depressed such that they surpass controls.

50. VISUAL SALIENCY RESPONSE IN THE SUPERFICIAL AND INTERMEDIATE SUPERIOR COLLICULUS. Janis Kan, Dr. Laurent Itti, Dr. Douglas Munoz

Cognitive and computational neuroscience postulates the existence of a visual saliency map and a priority map (combination of bottom-up saliency and top-down relevance) to guide orienting behavior. We hypothesize that the midbrain superior colliculus (SC) embodies the role of both a saliency map and a priority map compartmentalized in the superficial (SCs) and intermediate (SCi) layers, respectively. We compared monkey SCs and SCi firing rate and local field potential (LFP) in response to task-irrelevant but visually salient stimuli presented as a wide-field "pop-out" array. We randomly interleaved 0 to 4 pop-out items to examine how competition between items would affect saliency representation. We predicted that increasing the number of salient pop-out items from 1 to 4 would result in a systematic decrease in the saliency-evoked response at each pop-out location, because of increased competition. We found that 96% (23/24) of SCs neurons firing rate showed a reliable preference for the visually salient stimuli, but responded similarly in the presence of 1 to 4 pop-out items. A smaller percentage (75%; 24/32) of SCi neurons showed a preference for the salient but irrelevant stimuli, but their response was modulated by the number of pop-out items presented, possibly due to reflexive attentional mechanism. LFP responses of both layers displayed a biphasic response to presentation of an array stimulus that evolved to represent the pop-out item. This separation appeared earlier in the SCs than in the SCi.

51. INVESTIGATING PUPIL DYNAMICS IN PATIENTS WITH NEURODEGENERATIVE DISEASES. Jeff Huang, Brian C Coe, Matthew Smorenburg, Donald Brien, Sandra Black, Liz Finger, Morris Freedman, Tony Lang, Tanya Schmah, Rick Swartz, Carmela Tartaglia, Lorne Zinman, Douglas P Munoz, and the ONDRI Investigators

Brain loss in neurodegenerative diseases leads to impairments in various autonomic, motor, and cognitive functions. An easy-to-measure method that is increasingly used in clinical investigations to assess cognitive function is pupillometry. Pupil size is modulated by converging bottom-up sensory and top-down cognitive signals, as well as arousal and global luminance. Furthermore, the circuit for pupil control is suggested to be linked to the saccade generation system. We hypothesize that disruptions in neural circuitry due to neurodegeneration or brain injury can affect pupil control and its relationship to the saccade system. Here, we examined pupil dynamics in 6 neurodegenerative diseases (Alzheimer's disease, mild cognitive impairment, Parkinson's disease, amyotrophic lateral sclerosis, frontotemporal dementia, vascular cognitive impairment) and hypothesized that components of the pupil response should be altered due to neurodegeneration. Pupil size and eye position were recorded while subjects performed the interleaved pro-/anti-saccade task. The pupil constricted shortly after the presentation of the fixation cue following by dilation. Analysis revealed distinct differences between patient groups and age-matched controls in their pupil dynamics, including measurements of pupil constriction and dilation. The results demonstrated changes in pupil dynamics linked to neurodegeneration, showing that pupil measurements have the potential to serve as a behavioural biomarker for diagnosis of neurodegenerative diseases and tracking disease progression.

52. QUANTIFYING SENSORIMOTOR AND VISUOSPATIAL IMPAIRMENTS IN CHRONIC KIDNEY DISEASE PATIENTS: A PILOT STUDY. Jessica Vanderlinden, Dr. Stephen Scott PhD, Dr. Rachel Holden MSc, MD, and Dr. J. Gordon Boyd, MD, PhD Centre for Neuroscience Studies, Queen's University Kingston, Ontario Canada.

Background: Cognitive dysfunction is reportedly common in chronic kidney disease (CKD) patients, particularly in executive function, attention and memory. The majority of the assessments used to quantify these impairments are subjective screening tools for dementia. The KINARM (an objective robotic assessment) has been used to identify deficits that correlate with quality of life in patients with ischemic stroke. However, the quantitative neurocognitive phenotype of patients with CKD is unknown. Objective: To provide an objective and quantifiable description of neurological dysfunction in CKD patients. Methods: Patients underwent the following assessments: the KINARM, a robotic assessment that quantifies sensorimotor control of the upper limb, and the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), a traditional pen and paper assessment. This battery was completed before the initiation of dialysis. Results: To date, 20 out of the 35 stage 5 CKD patients enrolled have completed baseline assessments. The KINARM showed that 10/20 patients scored outside the normal range on tasks measuring executive and visuomotor. Seven out of 20 demonstrated impairments in attention. Regarding the RBANS, 6/20 showed impairments in the visuospatial domain, but the overall total cognitive score was within the normal range for the majority of patients (19/20). Conclusion: Quantifying visuospatial and sensorimotor impairments in CKD patients with the KINARM is feasible. The KINARM may identify more individuals with cognitive impairment. (Supported by Southeastern Ontario Medical Association's New Clinician Scientist Award and Queen's Dept. of Medicine Innovation Fund)

53. BRAIN TISSUE OXYGENATION AND QUANTIFIED NEUROLOGICAL OUTCOMES IN PATIENTS UNDERGOING CORONARY ARTERY BYPASS SURGERY. Joanna S. Semrau BSc, Stephen H. Scott PhD, Andrew G. Hamilton MD, Dimitri Petsikas MD, Darrin Payne MD, Gianluigi Bisleri MD, Tarit Saha MD, and J. Gordon Boyd MD PhD Centre for Neuroscience Studies

Background: Coronary artery bypass grafting (CABG) surgery is the most common type of open heart surgery performed in Canada. While this procedure can effectively treat coronary artery disease and improve myocardial perfusion, it may also expose patients to adverse neurological outcomes. Low intraoperative brain tissue oxygen (BtO2) may be associated with this cognitive decline. However, the lack of quantitative neurocognitive assessments has made this relationship unclear. In this study, we use the KINARM robotic system (BKIN Technologies) to generate a comprehensive neurological phenotype and define the role of BtO2 in post-operative neurological decline. Methods: Adult patients undergoing CABG were recruited for this single-center observational study. Patients' neurological function was assessed prior to and 3 months following their CABG surgery using the KINARM. Intraoperatively, BtO2 data was collected using near-infrared spectroscopy. Results: To date, 24 patients have completed pre- and post-operative testing. 58.3% of participants performed outside of the normal range on one or more KINARM tasks following CABG surgery. In particular, post-operative impairment was observed in sensorimotor tasks requiring additional attention and executive functioning. Poor performance on the reverse visually guided reaching task post-CABG also significantly correlated with lower intraoperative BtO2. Conclusions: Our results suggest that the KINARM can provide an objective and quantitative neurological assessment for CABG patients. The relationship between quantitative metrics of neurocognitive function and intraoperative brain tissue oxygen warrants further investigation. Funding: SEAMO Innovation Fund

54. THE ROLE OF DIFFERENTIAL NA+/K+ PUMP ISOFORM EXPRESSION IN HIGHER AND LOWER BRAIN REGIONS AND CONSEQUENCES FOR ISCHEMIA. Chloe Lowry, Michael Golod, Brian Bennett, R. David Andrew. Centre for Neuroscience Studies, Queen's University, Kingston, ON, Canada

Higher gray matter is more susceptible to acute ischemic injury than the lower brain. Discovering mechanisms contributing to the brainstem's resilience may inform targets for improved survival of higher brain regions. Our data mining suggests that the Na+/K+-ATPase 1a3 isoform is expressed in higher proportion in brainstem under basal conditions. It also pumps more efficiently under ischemic conditions than the 1a1 isoform which predominates in higher brain regions. We hypothesize that Na+/K+ pump isoform expression helps contribute to a region's susceptibility or resiliency to ischemia. Data from the Allen Brain Bank show proportionally greater 1a1 expression in higher brain regions. We analyzed 120 brain samples from 40 naïve mice across two different age cohorts and found significantly greater 1a3 mRNA expression in brainstem compared to neocortex. In contrast, we found significantly greater 1a1 mRNA expression in neocortex compared to brainstem. Our parallel protein expression studies are consistent with these findings. We are following up these results with analysis of 1a1 and 1a3 mRNA and protein levels from a chronically-stressed cohort of mice with age-matched controls. We suspect 1a3 expression will increase in the higher brain regions of behaviorally stressed mice. Understanding how Na+/K+-ATPase isoforms differ in their production in response to chronic metabolic and oxidative stress should yield insights into how such differences protect neurons during ischemic oxidative stress.

55. USING ADENO-ASSOCIATED VIRUS SEROTYPE 9 TO TREAT GM2 ACTIVATOR PROTEIN DEFICIENCY IN A MOUSE MODEL. Meera Vyas[1], K. Osmon[1], I. Ahmad[2], S. Kot[2], P. Thompson[3], S. J. Gray[4, 5] and J. S. Walia[1, 2, 3*1]Centre for Neuroscience Studies, Queen's University, Kingston, Ontario, Canada, K7L 3N6; [2]Department of Biomedical and Molecular Sciences, Queen's University, Kingston, Ontario, Canada, K7L 3N6; [3]Medical Genetics/Departments of Pediatrics, Queen's University, Kingston, Ontario, Canada, K7L 2V7; [4]Gene Therapy Center, University of North Carolina, Chapel Hill, North Carolina, United States; [5]Department of Ophthalmology, University of North Carolina, Chapel Hill, North Carolina, United States.

GM2 gangliosidoses are a group of neurodegenerative diseases. GM2 ganglioside is normally degraded in a cell's lysosomes by three gene products, *HEXA*, *HEXB*, and *GM2A*. A defect in any one gene can result in a deficiency of Hexosaminidase A (HexA) enzyme activity toward GM2-ganglioside, which then cannot breakdown. The AB-variant is characterized by a mutation in the *GM2A* gene that encodes the GM2-activator protein, a required co-factor for breakdown of GM2 gangliosides by the HexA protein. An effective viral vector known as Adeno-associated virus serotype 9 (AAV9) will be used. The aim of this study is to give a one-time treatment of AAV9.*GM2A* viral vector therapy at a dose of 1×10^{14} vector genomes per kilogram. Treatments were given intravenously to neonatal and adult mice. These mice undergo monthly behavioural testing, biochemical and molecular analysis, performed at 20 and 60-week end-points. We hypothesize that an optimized AAV9.*GM2A* treatment can correct the gene deficiency and phenotype of the AB-variant in mice. Preliminary behavioural data show no statistical significance, which is expected since the phenotypic characteristics in the GM2A deficient mouse model develop after 20 weeks. Biochemical data for the short-

term cohort showed a decrease in GM2 gangliosides, however not significant, of the treated mice when compared to vehicle treated. This research will provide a step forward towards our goal of human clinical gene therapy trials.

56. LOW BRAIN TISSUE OXYGENATION CONTRIBUTES TO THE DEVELOPMENT DELIRIUM DURING CRITICAL ILLNESS. Michael D. Wood, BA.[1]; David M. Maslove, MSc, MD[2,3]; John G. Muscedere, MD[2]; Andrew G. Day, MSc[4]; J. Gordon Boyd, MD, PhD[1,2,3] [1]Centre for Neuroscience Studies, Queen's University, Kingston, ON, Canada; [2]Dept. of Critical Care Medicine, Queen's University, Kingston, ON, Canada; [3]Dept. of Medicine, Queen's University, Kingston, ON, Canada; [4]Kingston General Hospital Research Institute, Kingston, ON, Canada

Objectives: Critical illness associated delirium is common, however, the underlying cause remains unknown. We tested the hypothesis that poor brain tissue oxygenation (BtO_2) during the first 24h hours of critical illness will correlate with the proportion of time spent delirious in the intensive care unit (ICU). We also aimed to explore the physiological determinants of BtO_2.
Methods: Adult patients were eligible for enrollment if they were admitted to the ICU within 24 hours of requiring invasive mechanical ventilation, and/or vasopressor support. BtO_2 was non-invasively recorded, using near-infrared spectroscopy (Casmed FORESIGHT, Caster Medical, Canada), for 24 hours after enrollment. Hourly vital signs and clinically ordered arterial and central venous blood gases were collected throughout BtO_2 monitoring. Patients were screened once daily for delirium with the confusion assessment method (CAM)-ICU. **Results:** BtO_2 and the proportion of time spent delirious did not result in a significant negative association (p = .168). However, our pre-planned analysis of dichotomized groups demonstrated that patients who spent the majority of their ICU stay delirious (≥50%) had significantly lower mean BtO_2 compared to non-delirious patients (p=0.008). BtO_2 correlated positively with central venous pO_2 (p=0.00003) and haemoglobin concentration (p = 0.001). Logistic regression analysis indicated that lower BtO_2, higher narcotic doses and a history of alcohol abuse were independent risk factors for delirium. **Conclusions:** This study demonstrates that low BtO_2 is an independent risk factor for the subsequent development of delirium. **Funding sources:** This work was funded by the Physician Services Incorporated and the Southeastern Ontario Academic Medical Organization New Clinician Scientist Program.

57. THE PRO-INFLAMMATORY CYTOKINE TUMOR NECROSIS FACTOR ALPHA EXCITES SUBFORNICAL ORGAN NEURONS. Nick J. Simpson[1,2], Alastair V. Ferguson[1,2]

Tumor necrosis factor alpha (TNFα) is a pro-inflammatory cytokine implicated in cardiovascular and autonomic regulation via actions in the central nervous system. $TNF\alpha^{-/-}$ mice do not develop angiotensin II (ANG II)-induced hypertension, and administration of TNFα into the bloodstream of rats increases blood pressure and sympathetic tone. Recent studies have shown that lesion of the subfornical organ (SFO) attenuates the hypertensive and autonomic effects of TNFα, while direct administration of TNFα into the SFO increases blood pressure, suggesting the SFO to be a key site for the actions of TNFα. Therefore, we used patch-clamp techniques to examine both acute and long-term effects of TNFα on the excitability of Sprague-Dawley rat SFO neurons. It was observed that acute bath application of TNFα depolarized SFO neurons and subsequently increased action potential firing rate. Furthermore, the magnitude of depolarization and the proportion of depolarized SFO neurons were concentration-dependent. Interestingly, following 24 hour incubation with TNFα, the basal excitability of SFO neurons was elevated. This effect was likely mediated the transient sodium current, as TNFα lowered its threshold of activation. These data suggest that acute and long-term TNFα exposure elevates SFO neuron activity, providing a basis for TNFα's hypertensive and sympathetic effects.

[1]Department of Biomedical and Molecular Sciences, [2]Center for Neuroscience Studies This work was supported by Canadian Institutes of Health Research

58. OXIDATIVE STRESS AND CHRONIC UNPREDICTABLE STRESS INTERACTIONS IN A MODEL OF PROGRESSIVE NEURODEGENERATION AND NEUROPSYCHIATRIC COMORBIDITIES. Nicole Czegledy and Brian Bennett. Centre for Neuroscience Studies. Queen's University Kingston, Ontario.

Oxidative stress is a common feature associated with cognitive impairment, anxiety, and depression. We have established Aldh2-/- C57BL/6 mice as an oxidative stress-based model of age-related memory loss and cognitive impairment. We performed a characterization of anxiety- and depression-like behaviours in our Aldh2-/- model. Three cohorts at different time points (3, 7, and 11 months of age) were subjected to a battery of behavioural tests including an assessment of mobility and exploration (open field test), anxiety-related behaviour (light/dark box and elevated plus maze), and depression-related behaviour (forced swim test and tail suspension test). Male and female Aldh2-/- mice were analyzed by sex and age, and exhibited increased anxiety-like behaviours that were first observed at 7 months of age compared to wild-type mice, and no significance difference or clear trend in depression-like behaviours. These data reveal a previously unreported behavioural changes in the Aldh2-/- model of AD-like cognitive impairment. Due to the role of the hippocampus in feedback inhibition of the hypothalamic-pituitary axis, we are currently performing a chronic unpredictable stress protocol to determine if differences in susceptibility to developing depression-like behaviours and deficits in memory within this model.

59. USING AN EMOTIONAL SACCADE TASK TO ESTABLISH BEHAVIOURAL BIOMARKERS IN ATTENTION-DEFICIT HYPERACTIVITY DISORDER AND BIPOLAR DISORDER. Rachel Yep, Donald C. Brien, Brian C. Coe, Alina Marin & Douglas P. Munoz Centre for Neuroscience Studies, Queen's University, Kingston, ON Canada

Despite distinct differences in age of onset and core symptoms, attention-deficit hyperactivity disorder (ADHD) and bipolar disorder (BD) share cognitive and emotional processing deficits that can make differential diagnoses difficult. In order to better characterize these two disorders, we compared ADHD and BD performance on a saccade paradigm designed to probe both executive functioning and emotional processing. We hypothesize that patient groups will be differentiated from controls on the basis of executive functioning performance, and patient groups will be differentiated from one another on the basis of emotional processing performance. Healthy control, ADHD, and BD participants performed an interleaved pro/antisaccade task in which the gender of emotional faces acted as the cue to perform either the pro or antisaccade. Saccadic reaction time and direction error performance was significantly worse on antisaccade trials compared to

prosaccade trials, with ADHD and BD groups making more direction errors than controls. The presentation of emotional face stimuli, particularly negatively valenced and neutral faces, differentially affected the performance of ADHD and BD groups. The findings presented here suggest that executive dysfunction is a key deficit in both patient groups, and that it is differentially impaired when recruitment of emotional processing systems is also required. Further characterization of how these processing systems interact in ADHD and BD could be used to develop psychiatric endophenotypes to help improve diagnoses.

60. STRUCTURE AND TIMING OF COMPUTERIZED COGNITIVE TRAINING TASKS IN SCHIZOPHRENIA: AN EEG ANALYSIS. Robyn Cardy, MSc Candidate; Dr. Felicia Iftene, MD, PhD, FRCPC

Recent efforts in the treatment of schizophrenia have focused on enhancing cognitive deficits, as research has demonstrated that cognitive impairments rather than symptoms, are associated with both concurrent and future functional outcome. A key challenge for Cognitive Remediation Therapy research is to determine what techniques and strategies provide the most benefit and how to effectively deliver them. The main purpose of this research is to determine which temporal structure for computerized cognitive training results in greater and more sustained electroencephalographical (EEG) change in patients with schizophrenia: repeated two-minute bursts of training and rest (for 20 minutes), or sustained 10 minutes of constant training (following 10 minutes of rest). Participants (n=24) were randomized into one of two training arms (burst or sustained training) and baseline, training, and testing EEG recordings were compared for superiority, with satisfaction questionnaires administered post-testing to determine contentment with training arm administered. Baseline symptoms of schizophrenia are assessed before training using a self-report measure to determine any between-group differences. A satisfaction questionnaire administered post-testing to determine contentment with training received. The results of this research will help inform effective and efficient structuring of of cognitive training modules for schizophrenia to optimize delivery of cognitive remediation therapy. By identifying the immediate functional brain wave changes of a single “dose” of cognition training in schizophrenia subjects, results will help determine the validity of the NeuroNation Cognitive Training Program within this population. Lastly, this research will determine the more preferred structure and timing of cognitive training modules, to improve program adherence, increase patient satisfaction of therapy, and ultimately tailor cognitive training to the needs and preferences of schizophrenia patients.

61. INVESTIGATING THE EFFECTS OF RAPAMYCIN AND PREDNISONE ON THE HEIGHTENED IMMUNE RESPONSE FOLLOWING AAV9-HEXM TREATMENT IN SANDHOFF MICE. Shalini Kot, K.J.L. Osmon, E. Woodley, P. Thompson, M. Vyas, I. Ahmad, Z. Chen, M. Mitchell and J.S. Walia

Sandhoff disease (SD) is a neurodegenerative disorder caused by the toxic accumulation of GM_2 gangliosides in the brain. The β-hexosaminidase A enzyme (HexA), consisting of an α and β subunit, is involved in the catabolism of GM_2 gangliosides. SD is caused by a defective β-subunit, which in turn leads to a deficient HexA enzyme. A recently published isoenzyme of HexA, known as HexM, can catabolize GM_2 gangliosides efficiently. The gene encoding for HexM fits the cargo capacity of the self-complementary adeno-associated virus 9

(scAAV9). A previous study, using the AAV serotype 9 (AAV9) vector expressing HexM, showed successful long-term correction of SD in the murine model. However, the use of scAAV9-*HEXM* has the potential to produce a heightened immune response, which can decrease the clinical outcome in treatment for this disease. In order to improve the treatment benefits of gene therapy, experiments are ongoing to analyze the use of immunosuppressants, rapamycin and prednisone, in conjunction with gene therapy treatment to counteract the heightened immune response. The outcomes of this study should provide insight into whether or not these immunosuppressants, alone or in combination, can reduce the immune response to HexM delivered via gene therapy. This study may prove to be the final stepping-stone towards clinical gene therapy for the treatment of SD.

62. AN EVALUATION OF A STIGMA MANAGEMENT PSYCHOEDUCATIONAL AND BEHAVIOURAL MODIFICATION COURSE FOR PEOPLE WITH MOOD AND ANXIETY DISORDERS. Shamik Sen and Roumen Milev. Department of Neuroscience, Queen's University Kingston, Ontario Canada.

The Overcoming Stigma in Mood and Anxiety Disorders (OSMAD) course has been designed to help people with mood and anxiety disorders better manage self-stigma, improve feelings of self-efficacy, and promote recovery. The current study aims to evaluate the efficacy of this group-based, psychoeducational and behavioural modification intervention in reducing the impact of mental-illness-related stigma. Primary outcomes are measured through qualitative analysis of focus group discussion regarding experiences with the course and the perception and experience of stigma. An additional pre-test-post-test design measures changes to various psychosocial impacts of stigma for participants with mood and/or anxiety disorders using a modified 12-item Stigma Impact Scale from the Inventory of Stigma Experiences. Quantitative results from the pilot trial of OSMAD showed significant decreases in stigma experiences in areas of life that are under personal control, including: self-esteem, social contacts, personal goals, family relationships and physical health. Qualitative analysis is currently underway to generate a greater depth of understanding regarding themes revolving around the course's contribution to recovery and in understanding how to reduce structural stigma regarding areas of life outside of personal control. This study will be an important step towards developing evidence-based interventions to overcome self-stigma and manage social stigma to have a full and meaningful life.

63. SPREADING DEPOLARIZATION EVOKED BY OXYGEN-GLUCOSE DEPRIVATION IN CEREBRAL CORTICAL SLICES OF THE FROG. V.Donovan, R.D. Andrew. Centre for Neuroscience Studies

Anoxia in mammals and insects induces an abrupt shutdown of higher CNS gray matter as a result of spreading depolarization (SD) but it is unclear if SD is generated in the cerebral cortex (CC) of lower vertebrates. In this study, the effects of oxygen glucose deprivation (OGD) on live coronal brain slices from frogs was compared to rats to better understand the evolution of SD and susceptibility of a cold-blooded species to SD. We examined whether frog CC can generate SD and if so, its propensity to initiate compared to rat. Light transmittance (LT)

imaging was used to determine SD onset time and neuronal damage in response to OGD, ouabain (100 uM) or elevated $[K^+]_o$, at several temperatures. Our aim is to establish a connection between these two species in order to find evidence for an evolutionarily conserved response in the higher brain of mammals as seen in evolutionary older species. Our findings show that the capacity to generate SD in the cerebral cortex evolved early in vertebrate evolution, but that the propensity to initiate SD appears greater in rat versus frog at 35 ^oC.

64. THE SEARCH FOR EFFECTIVE CORRECTION- SYSTEMIC HEXOSAMINIDASE HYBRID GENE THERAPY ON NEONATAL AND ADULT SANDHOFF MICE. Karlaina JL. Osmon[1], E. Woodley[2], P. Thompson[3], M. Vyas[1], S. Karumuthil-Melethil[4], John G. Keimel[5], S. J. Gray[4, 6] and J. S. Walia[1, 2, 3*] [1]Centre for Neuroscience Studies, Queen's University, Kingston, Ontario, Canada, K7L 3N6; [2]Department of Biomedical and Molecular Sciences, Queen's University, Kingston, Ontario, Canada, K7L 3N6; [3]Medical Genetics/Departments of Pediatrics, Queen's University, Kingston, Ontario, Canada, K7L 2V7; [4]Gene Therapy Center, University of North Carolina, Chapel Hill, North Carolina, United States; [5] New Hope Research Foundation, North Oaks, Minnesota, USA [6]Department of Ophthalmology, University of North Carolina, Chapel Hill, North Carolina, United States.

G_{M2}Gangliosidosis are neurodegenerative disorders caused by a deficiency of HexosaminidaseA enzyme (HexA). HexA (α- and β-subunits) is the only enzyme able to catabolize G_{M2}gangliosides (GM2); in the central nervous system, deficiency of HexA leads to GM2 accumulation, which causes neuronal death. In our previous works, a hybrid subunit was constructed to replace HexA, integrating catalytic properties of the α-subunit, and stabilization sites of the β-subunit. The hybrid μ-subunit, coded by *HEXM*, homodimerizes forming HexM, which catabolizes GM2. In the current study, *HEXM*, packaged into adeno-associated virus 9 (AAV9), was given intravenously to adult and neonatal (NEO) Sandhoff (SD) mice to assess the efficiency of systematic treatments at different administration ages. We injected 2.5E14vg/kg dose in NEO mice. Two doses were used in the adult HEXM treated group, 5E14vg/kg (high dose, HD) and 1.25E14vg/kg (medium dose, MD). We hypothesized that the HEXM treatment would significantly improve survival, locomotion, and biochemical outcomes. Although untreated SDmice reach humane endpoint at 16 weeks old, the NEO, HD, and MD treated SDmice survived significantly longer, an average of 44.7, 58.8, and 40.6 weeks, respectively. Biochemical data shows an increase in enzyme activity and a decrease in GM2 storage in the *HEXM* treated mice. Behaviourally, *HEXM* treated mice perform better than controls. Results from this study provide proof of the corrective abilities of AAV9/*HEXM* at both the neonatal- and adult-age administrations.

65. EXAMINING THE EFFECT OF DOPAMINERGIC TREATMENT ON COGNITIVE FUNCTION IN PARKINSON'S PATIENTS DURING AN OCULOMOTOR STRATEGIC DECISION-MAKING TASK. Parr, Ashley, Riek, H., Coe, B., Pari, G., & Munoz, D. Department: Centre for Neuroscience Studies

During competitive games like rock-paper-scissors (RPS), each player's actions and associated outcomes change dynamically based on their opponent's actions. Optimizing strategies requires choosing among several actions, the likelihood of which is adjusted dynamically based on reinforcement information, a process involving frontostriatal networks. Dopamine (DA) medication alters learning rates in reinforcement learning tasks, potentially contributing to impulse control disorders and maladaptive decision-making in patients. Our goal was to characterize reinforcement learning deficits, the effects of DA treatment and medication-induced cognitive dysfunction, in PD during a strategic game analogous to RPS. Finally, we aimed to investigate dysfunction across multiple motor systems, namely, those controlling saccadic eye movements and hand movements. PD patients (Hoehn & Yahr stage 1-3) and age-matched controls competed in a game of RPS against a computer opponent that exploited biases in choice patterns. Participants maximized reward by minimizing predictabilities in choice sequences. Choices were indicated with either a saccade or button press. Both groups completed 2 sessions; patients both on- and off- medication. Reinforcement learning processes and predictabilities in choice sequences were examined, and behavior was correlated with neurocognitive scores (i.e., The Baratt Impulsiveness Scale) and motor scores (Unified Parkinson's Disease Rating Scale (UPDRS)). Patients were impaired in choosing optimally during RPS in the saccade condition, particularly when on dopaminergic medication compared to off. Patients were more variable, exhibited more predictable choice patterns, and had lower overall reward rates compared with controls in the saccade condition. Patients performed better during the button-press compared to the saccade condition in nearly all aspects of RPS, suggesting greater dysfunction within the oculomotor loops through the basal ganglia. We propose a new tool to investigate the effect of dopaminergic treatment on cognition in PD, which could lead to novel insights into optimizing treatment and maximizing cognitive function. Further investigation into individual differences in the PD group could provide insight into the traits that predispose certain patients to impulse control disorders.

Other

66. USE OF ANIMATIONS AS AN ACTIVE TEACHING TOOL IN DEVELOPMENTAL ANATOMY. Sidra Shafique, Ron A. Easteal, Conrad Reifel. Department of Biomedical and Molecular Sciences, Faculty of Health Sciences, Queen's University, Kingston, Ontario, Canada.

Introduction: Education in Mammalian Embryology is challenging due to complicated developmental morphological transformations. Traditional teaching or lecturing, commonly used to teach this discipline, may serve more effectively if combined with active teaching tools such as computer-aided animations (CAA). It was hypothesized that traditional teaching combined with CAA improves student learning experience as compared to traditional teaching alone in the discipline of Developmental Anatomy. Methods: Thirty-two students of a fourth year Mammalian Embryology course participated in this study. The study was designed in six modules, each consisting of one to two animations related to a topic in the course material. Data were collected through pre-test and post-test questionnaires. Results: Participants supported (*p=0.028*) the traditional teaching combined with animations as compared to traditional teaching alone. It was indicated that CAA helped in better understanding the concepts with sequential steps (*p=0.001*), three dimensional visualization of images (*p=0.035*), and improved their interest in Embryology as a subject (*p=0.009*). Qualitative data analysis resulted in the following themes: CAA is a helpful and great visual tool being useful for understanding three-dimensional concepts, and traditional teaching is mostly teacher centered, needs better communication strategies and supplement / adjunct tools. Conclusion: Traditional teaching in combination with computer-aided animations may improve the learning experience, especially at the conceptual level, in the discipline of Developmental Anatomy.

67. MISSING DATA IN COMPLEX SURVEYS: AN OVERIVEW OF MULTIPLE IMPUTATION AND WEIGHTED APPROACHES. Michael A. Reaume and Michael A. McIsaac**.** Department of Public Health Sciences, Queen's University**,** Kingston, Ontario, Canada

Missing data are common in public health research, and the inability to properly account for these occurrences can lead to biased results and erroneous conclusions. Many techniques have been developed to address unplanned missing data, such as multiple imputation and likelihood weighting. The former approach involves creating complete datasets by adding values to the missing fields (in a way that preserves the associations observed in the dataset), while the latter approach assigns more importance to observations that are similar to those with missing values (which are then excluded from the analysis). Multiple imputation estimators are more efficient than weighted likelihood estimators, but they usually require the specification of a parametric model, which is not always possible (for example, when the sampling design is complex or when there are multiple sources of missing data). These techniques have been explored extensively for use during the analysis stage. However, there is a gap in the literature concerning the implications of unplanned missingness during the design stage, especially in the context of two-phase studies, where subsamples are taken from an initial sample for further investigation. The objective of this project is two-fold: 1) perform a literature review on the analysis of complex surveys with missing data (with an emphasis on likelihood weighting and multiple imputation), and 2) derive optimal sampling designs for weighted likelihood analyses of two-phase study designs. Funding: Natural Sciences and Engineering Research Council of Canada (NSERC), Queen's University.

68. EVALUATION OF A WEB-BASED MODULE AND AN OTOSCOPY SIMULATOR IN TEACHING EAR DISEASE. Vincent Wu BHSc1 and Jason A. Beyea MD PhD FRCSC[1] [1]Department of Otolaryngology, Hotel Dieu Hospital, Queen's University, Kingston, Ontario. Queen's University Clinical Simulation Centre

Background: Ear diseases such as acute otitis media are particularly difficult to diagnose. The recent development of otoscopy simulation aims to strengthen the diagnostic ability of trainees without the need to practice on human volunteers. Objective: To investigate whether otoscopy simulation (OS), as compared to a web-based module (WM) and standard classroom instruction (SI), improves diagnostic accuracy and otoscopy clinical skills. Subjects and Methods: 54 medical students were recruited to a randomized controlled trial. They were randomized to either: 1) OS, 2) WM, or 3) SI (control group). All students underwent baseline testing of diagnostic accuracy (using 25 ear pathologies) and otoscopy clinical skills. Immediately following each intervention and 3 months later, testing was repeated. Results: Immediately post-intervention, OS and WM scoring significantly higher than SI on diagnostic accuracy (p<0.05). This improvement persisted at 3-months for the OS group (p<0.05). For clinical skills, OS scored significantly higher than WM and SI (p<0.05), an effect that persisted at 3-months (p<0.05). Conclusion: In this randomized controlled trial, otoscopy simulation and web modules significantly improve diagnostic accuracy for diseases of the ear. Otoscopy simulation has the additional benefit of improving otoscopy clinical skills.

Protein Structure and Function

69. FUNCTIONAL ANALYSIS OF THE REGIONS CONNECTING THE MEMBRANE SPANNING DOMAINS TO THE NUCLEOTIDE BINDING DOMAINS OF MRP1. Emma E. Smith, Gwenaëlle Conseil and Susan P.C. Cole. Department of Pathology and Molecular Medicine

Multidrug resistance protein 1 (MRP1/*ABCC1*) confers multidrug resistance in tumour cells by reducing intracellular drug accumulation through active efflux. MRP1 also transports many endobiotic organic anions including estradiol glucuronide (E2Gluc). MRP1 has three membrane-spanning domains (MSD) (which form the translocation pathway), and two nucleotide binding domains (NBD) (that bind /hydrolyze ATP). MSD1/2 and NBD1/2 are linked by connecting regions (CR) 1 and CR2, respectively, which are not well characterized. The objective of this study is to explore the role of CR1/2 in conveying information between the NBDs and MSDs, and allowing conformational changes essential for transport. Alanine substitutions of six strategically selected CR1 and CR2 residues have been generated by PCR-based mutagenesis, and their effects on MRP1 levels, cellular localization and activity investigated. To date, immunoblots indicate that total levels of CR2 mutants P1275A and G1291A are comparable to wild-type MRP1, whereas W1287A levels are reduced by 80% ($p<0.05$). Measurement of MRP1- dependent [3H]E2Gluc uptake into membrane vesicles show that neither P1275A or G1291A substantially affect MRP1 activity. Immunofluorescence and cell surface biotinylation indicate that all three mutants are trafficked to the plasma membrane. Thus, although W1287A is poorly expressed, its trafficking is not grossly disrupted, indicating a novel and unexpected role for CR2-Trp^{1287} in MRP1 biosynthesis. Ongoing studies are aimed at comparing the relative roles of CR1 and 2 in MRP1 function. Supported by CIHR grant MOP-133584

70. NON-SYNONYMOUS VARIANTS OF THE HUMAN ORGANIC ANION TRANSPORTER MRP4 (*ABCC4*) IMPAIR PROTEIN LEVELS AND TRAFFICKING TO THE PLASMA MEMBRANE. Gwenaëlle Conseil[1], Katrin Ziems[1], Mayukh Banerjee[2], Elaine M. Leslie[2] & Susan P.C. Cole[1] [1] Div of Cancer Biology & Genetics, Queen's University Cancer Research Institute, Kingston, ON [2] Dept of Physiology, University of Alberta, Edmonton, AB

Multidrug resistance protein 4 (MRP4) (*ABCC4)* is a 170 kDa organic anion transporter that mediates the efflux of endo- and xenobiotics across the plasma membrane, at the expense of ATP hydrolysis. Substrates include signaling molecules, anticancer and antiviral drugs as well as steroid conjugates. *ABCC4* is a polymorphic gene with ~500 missense mutations (non-synonymous single nucleotide polymorphisms (nsSNPs)) reported to date. The objective of this study was to determine whether three selected *ABCC4* nsSNPs (V776I, C956S and V1071F) affect the levels and/or activity of MRP4. Immunoblotting showed that V776I and C956S levels are similar to wild-type MRP4 in total cell extracts, but are significantly reduced at the plasma membrane, indicating trafficking of these mutants is impaired [1]. By comparison, levels of V1071F (but not V1071I/L) are substantially decreased in both total and plasma membrane preparations from transfected cells. Co-localization studies by immunofluorescence microscopy with proteasome, lysosomal and other markers and inhibitors failed to identify a single subcellular localization of the defective V1071F (V776I, C956S [1]). Levels of all three MRP4 mutants were increased, and proper routing to the plasma membrane enhanced by exposure

to the chemical chaperone 4-phenylbutyrate (4-PBA). Preliminary functional analyses indicate that the three 4-PBA-rescued mutants retain varying degrees of transport activity. We conclude that these three *ABCC4* nsSNPs have the potential to impact MRP4 activity with possible physiological and/or pharmacological consequences.
[1] Banerjee et al. (2016) Biochem Pharmacol. 120:72-82 Supported by CIHR grants (MOP-133584; MOP-106513; MOP-272075), the Alberta Cancer Foundation (No. 25842) and Prostate Cancer Fight Foundation (KGH).

71. ENGINEERING A MULTI-ENZYME COMPLEX WITH ENHANCED AGAROSE-DEGRADING PROPERTIES USING CARBOHYDRATE-ACTIVE ENZYMES. Keegan B. Turner-Wood, Steven P. Smith. Department of Biomedical and Molecular Sciences

Lignocellulosic biomass is a vast and largely untapped carbon reservoir, representing an abundant source of energy. The repeating sugars that make up polysaccharide chains are held together in recalcitrant crystalline lattices which require specialized carbohydrate active enzymes (CAZymes) to cleave. Many bacteria have evolved CAZymes, allowing them to degrade polysaccharides. To further enhance their digestive efficiency, an extracellular protein complex possessing the most catalytically active polysaccharide degrading machinery known to man has evolved in terrestrial bacteria. This cellulose degrading complex is termed a cellulosome; although marine bacteria don't construct a molecular scaffold, their enzymatic function is comparable given their substrate similarity. As such, the engineering of a chimeric scaffold composed of binding proteins based on the cellulosome has been proposed, onto which a series of agarose degrading enzymes will be mounted. The association of CAZymes to a molecular scaffold has been shown to greatly enhance their catalytic ability by increasing their synergistic digestion via proximity. Furthermore, the inclusion of a carbohydrate binding module, which attaches the entire protein complex to a target polysaccharide, greatly increases the enzymatic activity of the complex. Altering the configuration of the molecular scaffold allows for optimization of the complex's activity. Information on the synergistic behaviour of independent and complex associated agarases will allow for the construction of an efficient agarose degrading protein complex. (supported by NSERC)

72. SOLUTION CHARACTERIZATION OF THE COHESIN-DOCKERIN DUAL BINDING MODE: A HIGH AFFINITY PROTEIN-PROTEIN INTERACTION CRITICAL FOR CELLULOSOME ASSEMBLY. Alison L. Upsdell, Holly L. Spencer, David N. Langelaan, Steven P. Smith Department of Biomedical and Molecular Sciences, Queen's University

The anaerobic bacterium *Clostridium thermocellum* efficiently hydrolyzes lignocellulose via a multi-enzyme complex termed the cellulosome. Cellulosome assembly involves several carbohydrate-active enzymes docking onto a scaffoldin subunit, through a high-affinity interaction between the enzyme-borne type-I dockerin modules and scaffoldin-borne type-I cohesin modules. Type-I dockerins comprise a duplicated 22-residue sequence and a corresponding structural symmetry, suggesting that they can contact type-I cohesin in two orientations 180° apart. X-ray crystallographic studies reveal both binding modes are possible but substituting the critical molecular determinants Ser45 and Thr46 with alanine residues is required. A dual binding mode has not been shown for wild-type type-I dockerins in solution, with our NMR data demonstrating that both wild-type bound conformations occur simultaneously and equally in solution. Implementing Ser11Ala/Thr12Ala and Ser45Ala/Thr46Ala versions of the type-I dockerin allows us to select for

the two orientations that are consistent with crystallography and serve as controls for each binding mode. The mutant spectra display a subset of resonances influenced by cohesin and these residues pertaining to each conformation are collectively affected for wild-type dockerin. Wild-type dockerin resonances are intermediate between those of the mutant dockerin modules, suggestive of an average of the two populations and thus indicative of a dual binding mode. The possibility of two binding orientations overcomes the steric hindrance inherent to multi-protein complex assembly and the selection of a particular mode enhances designer cellulosomes. (Supported by NSERC)

Reproductive and Sexual Function

73. EFFECT OF CORM-A1 ADMINISTRATION ON PLACENTAL HYPOXIA LEVELS IN CD-1 MICE. Megan Dickson (B.Sc. Candidate)[1], Karalyn McRae[1], Nichole Peterson[1], Graeme Smith[1,2]. [1]Department of Biomedical and Molecular Sciences, Queen's University, Kingston, Ontario [2]Department of Obstetrics and Gynaecology, Kingston General Hospital, Kingston, Ontario

Preeclampsia (PE) is a hypertensive disorder that complicates 5-7% of pregnancies. Research suggests that CO may protect against PE. However, CO is known to cause hypoxia. The objective was to identify at which dose hypoxia in the mouse placenta occurs after injection of a carbon monoxide releasing molecule (CORM-A1). On gestational day (GD) 10.5, pregnant CD-1 mice (Charles River, USA) were given an IP injection: one of saline, 10 mg/kg inactive CORM-A1 (iCORM-A1) or CORM-A1 (5 mg/kg, 8 mg/kg, or 10 mg/kg). Blood was collected 15 minutes post-injection. On GD11.5 an IP injection of pimonidazole (Hypoxyprobe™) was given before euthanasia for detection of placental hypoxia using IHC. %COHb by group was compared with the Kruskal-Wallis Test and Dunn's Multiple Comparisons. Resorption rate was calculated (# resorptions / # implantation sites per group) with 95% confidence limits (Fishers Exact). Blood %COHb in saline and iCORM-A1 controls were 0.81%±0.11% (n=3) and 0.84%±0.26% (n=3), respectively. 5 mg/kg, 8 mg/kg and 10 mg/kg CORM-A1 treatment raised the %COHb to 1.96%±1.10% (n=4), 4.29%±0.84% (n=3), and 5.55%±1.35% (n=3), respectively (comparison to saline; p-values >0.05, >0.05, <0.05). No association between CORM-A1 exposure and resorption rate was observed. There were no differences in hypoxia levels (8 mg/kg CORM-A1 vs iCORM-A1), based on visualization using fluorescence and light microscopy. Future work may prove the safety and efficacy of CO as a therapeutic for PE. Funding: CIHR

Therapeutics and Toxicology

74. A NEW TREATMENT PARADIGM FOR NEURODEGENERATION: ISOTOPE-REINFORCED POLYUNSATURATED FATTY ACIDS MITIGATE COGNITIVE IMPAIRMENT IN A MOUSE MODEL OF SPORADIC ALZHEIMER'S DISEASE. Ahmed Elharram[1], Nicole Czegledy[1], Michael Golod[1], Ginger L.Milne[2], Erik Pollock[3], Mikhail S. Shchepinov[4], and Brian Bennett[1]. Department of Biomedical and Molecular Sciences and Centre for Neuroscience Studies, Queen's University, Kingston Ontario Canada[1]; Vanderbilt University, Nashville, TN[2]; University of Arkansas, Fayetteville, AR[3]; Retrotope, Inc. Los Altos, CA[4]

Polyunsaturated fatty acids (PUFAs) are essential nutrients that have to be supplied through the diet, and which are then incorporated into lipid structures throughout the body. Lipid peroxidation (LPO) of PUFAs is detrimental to cells, and toxic aldehyde markers of LPO, e.g. 4-hydroxynonenal (HNE) are elevated in several neurodegenerative diseases, including Alzheimer's disease (AD). To stabilize but minimally change critical PUFAs, incorporation of deuterium at *bis*-allylic positions (D-PUFAs) utilizes the 'kinetic isotope effect' to inhibit the initiation phase of LPO. We assessed the effects of a D-PUFA-enriched diet in an oxidative stress-based mouse model of cognitive impairment based on gene deletion of aldehyde dehydrogenase 2 (ALDH2). ALDH2 is important for the detoxification of endogenous aldehydes such as HNE, and $Aldh2^{-/-}$ mice exhibit oxidative stress, a progressive decline in recognition and spatial memory, anxiety-like behavioural changes, and a number of AD-like pathological changes. Multiple cognitive function tests demonstrated mitigation of cognitive impairment in $Aldh2^{-/-}$ mice fed a D-PUFA diet to a level of cognitive performance similar to wildtype mice, whereas no such changes occurred in $Aldh2^{-/-}$ mice fed the control (H-PUFA) diet. In addition, the D-PUFA diet markedly reduced the levels of lipid peroxidation markers (F_2-isoprostanes) in cortex and hippocampus. These data, coupled with early signs of efficacy in a recent Phase I/II clinical trial of D-PUFAs for the treatment of Friedreich's ataxia (a rare neuromuscular disorder characterized by excessive mitochondrial LPO) suggest D-PUFAs represent a promising new strategy to prevent cellular damage due to oxidative stress-induce LPO in a broad range of pathological conditions.

75. HISTOLOGICAL ANALYSIS TO EXPLAIN POOR CARDIOVASCULAR OUTCOMES IN RESPONSE TO LOW DOSE ISOPROTERENOL. Ana Nikolovska, Terence R.S. Ozolinš, & Louise M. Winn. Department of Biomedical and Molecular Sciences, Queen's University, Kingston, ON.

Congenital heart defects (CHD) are the most common birth anomaly occurring in 1-2.5% of births. The dimethadione (DMO)-induced model of CHD is an effective model to study the incidence and resolution of CHD as well as the response to a cardiovascular stressor in adulthood. In this experiment, the control groups were administered the vehicle and an *ad libitum* diet (*ad-lib* control) or the vehicle and a pair-fed diet (pair-fed control) while the treated group was administered a total of 4 doses of 300 mg/kg DMO p.o. during gestational days 9 and 10. However, upon encountering some unusual results with respect to the control group, the focus of the study was shifted to determine a possible explanation for their poor response to a low dose of isoproterenol (INE), a β-adrenergic agonist. Fifty percent of the rats born to the mothers in the *ad-lib* control and pair-fed control groups died within 10 minutes of INE administration. The hearts of the remaining 50% exhibited signs of cardiac hypertrophy. Preliminary analysis of the postnatal day 4 female rat hearts revealed a higher than normal incidence of CHD ranging from a thin right ventricular wall to a double apex. Further quantitative analysis must be done in order to confirm these findings.

76. THERAPEUTIC IMPACT OF FERMAGATE ON VASCULAR CALCIFICATION IN A RAT MODEL OF CHRONIC KIDNEY DISEASE. Jeronimo PS[1], Pruss C[1], Laverty K[1], Svajger B[1], Turner M[1], Ward E[1], Petkovich M[1], Holden RM[2], Adams MA[1] Department of Biomedical and Molecular Sciences (1) and Department of Medicine (2), Queen's University, Kingston, Ontario, Canada

Hyperphosphatemia is an independent risk factor in chronic kidney disease (CKD) and plays a critical role in vascular calcification (VC), the accrual of calcium and phosphate as hydroxyapatite that negatively affects cardiovascular hemodynamics. Maintenance of serum phosphate levels is a key therapeutic target in CKD. Fermagate is a phosphate binder that limits the absorption of phosphate in the gut and contains readily absorbable magnesium, which studies have shown can attenuate VC. Male Sprague Dawley rats (n=33) were fed a low phosphate adenine-containing diet for 4-6 weeks to induce CKD. Rats were then fed 10 g of high phosphate food twice a day for 25 days. Treatment rats were dosed with Fermagate with the first 10 g of food each day. Blood phosphate, magnesium, calcium, PTH and FGF-23 were measured at 5 time points. At sacrifice, 15 vessels were removed, and tissue phosphate, magnesium and calcium were measured. Overall serum phosphate was significantly lower ($p<0.0001$) and magnesium was significantly elevated ($p<0.0001$) in the fermagate-treated rats compared to controls. Rats on Fermagate had lower PTH compared to controls ($p<0.01$). Overall, the proportion of vessels that calcified (phosphate >50nmol/mg tissue) on Fermagate was significantly lower than in controls ($p<0.0001$). These findings demonstrate the ability of fermagate to lower serum phosphate and increase serum magnesium, which significantly reduced susceptibility to VC in a model of CKD.

77. EMBRYOPATHIES INDUCED BY *IN VIVO* VALPROIC ACID EXPOSURE TO MURINE EMBRYOS. Sidra Shafique[1], Louise M. Winn[1,2]. Department of Biomedical and Molecular Sciences, Queen's University, Kingston[1] School of Environmental Studies, Queen's University, Kingston[2]

Introduction: Valproic acid (VPA) is a widely prescribed antiepileptic drug and an effective treatment of Bipolar disorders, neuropathic pain and cancer. VPA is embryotoxic at therapeutic dose and a known histone deacetylase inhibitor resulting in altered acetylated state of histones and other cell proteins. Research done in our lab has shown embryopathies by VPA in CD-1 mouse embryo culture and perturbations in CBP/p300 expression in P19 cells. The embryotoxicity caused by therapeutic dose of VPA and the role of altered CBP/p300 HATs remains unknown following in utero/in vivo exposure. Hypothesis: Following *in utero* VPA exposure, as an adaptive response to histone diacetylase inhibition, the CBP/p300 expression is reduced. *In vivo* exposure to VPA results in open neural tube defect, failed turning of mouse embryo and growth retardation as observed in embryo culture. Methods: The study group of pregnant CD-1 mice were exposed to 400mg/kg VPA and controls were injected with vehicle by subcutaneous injection. After 24 hour mice, study and control group, were sacrificed and embryos collected. The morphological analysis was done under dissecting microscope on GD10. The CBP/p300 expression analysis will be done by Western Blot and RT-qPCR. Results: In vivo 24 hour exposure of VPA (n=3, total number of embryos = 46) indicated that VPA results in growth restriction by shortened crown rump length (*p=0.019),* causes open neural tube defect (*p=0.0084)* and failure of turning in mouse embryos (*p=0.0138).* Conclusion: These results validate the morphological embryopathies observed in embryo culture. Further analysis will be first to evidence the perturbations in CBP/p300 level and reveal the mechanism of VPA embryotoxicity.

78. INVESTIGATING PERTURBATIONS OF FETAL TOPOISOMERASE IIA FOLLOWING BENZENE EXPOSURE. Trent H. Holmes and Louise M. Winn. Department of Biomedical and Molecular Sciences, Queen's University Kingston, Ontario Canada

Recent studies suggest that maternal exposure to benzene during fetal development may lead to leukemia in offspring [1]–[3]. While the etiology of fetal benzene-induced leukemia is unknown, benzene is known to affect the critical DNA repair enzyme topoisomerase IIα (TOP2a) [4]–[6]. To date no studies have investigated the effects of benzene on fetal TOP2a. This research will determine if and how benzene affects fetal TOP2a through two aims. Aim 1 will evaluate the effects of the toxic benzene metabolite, benzoquinone (BQ), on fetal TOP2a in gestational day (GD) 14 mouse fetal liver cells following exposure for 6 or 24 hours [7]. Three TOP2a parameters will be measured: (1) TOP2a activity will be quantified using a TopoGen TOP2a activity kit, (2) DNA-adduct formation will be measured using a dot-blot technique, and (3) TOP2a expression will be quantified using western blotting. Aim 2 will examine the effects of in utero benzene exposure on fetal TOP2a. CD-1 pregnant dams will be exposed (200 mg/kg or corn oil control) via IP intraperitoneal injection every other day from GD 8-14 and fetal livers collected 2, 6, and 24 hours after final dosage. TOP2a will be measured as per aim 1. These experiments will help identify the effects of benzene on fetal TOP2a. Support: CIHR

79. EFFECTS OF POSTNATAL ADRENERGIC RECEPTOR STIMULATION ON LATENT CONGENITAL HEART DEFECTS IN MALE SPRAGUE DAWLEY RATS. Rebecca D. Maciver, Michael A. Adams, Louise M. Winn & Terence R. S. Ozolinš. Department of Biomedical and Molecular Sciences, Queen's University, Kingston, ON.

Congenital heart defects (CHD) are the most prevalent birth defect, occurring in approximately 1% of births, with 80% spontaneous resolution by one year of age. We hypothesize that hearts from individuals with resolved CHD are more susceptible to pathophysiological responses when exposed to stressors later in life. Using an animal model, we have demonstrated that female rats born with CHD that resolve by adulthood have a maladaptive response to the burden of pregnancy; how male rats with resolved CHD respond to cardiac stressors is unknown. Time-mated Sprague Dawley rats were dosed with 300 mg/kg dimethadione via oral gavage every 12 hours from gestational days 9-10 to produce offspring with a 50% incidence of CHD. Echocardiography was performed on postnatal days (PND) 4, 21, and 56 to evaluate heart structure and function in male offspring prior to cardiac challenge. To stress the heart, rats were intermittently administered 0.01 mg/kg isoproterenol, a beta-adrenergic agonist, by subcutaneous injection. Hearts were assessed longitudinally for function, hypertrophy and threshold for reversibility. In the period prior to cardiac challenge, structural and functional differences were apparent between experimental groups as measured by ultrasound, suggesting that males may not resolve CHD to the same extent as females. When accounting for these baseline differences, preliminary analysis of cardiac structural and functional measures point toward maladaptive responses to the cardiovascular stressor. Ongoing assessment will provide a more comprehensive analysis of the long-term vulnerabilities of CHD.

Women's and Children's Health Research

80. MENADIONE AS AN ALTERNATIVE METHOD OF ENDOGENOUS CARBON MONOXIDE PRODUCTION IN MICE.
Chioma U Odozor[1], Nichole Peterson[1] and Graeme N Smith[1,2]. [1]Department of Biomedical and Molecular Sciences, Queen's University, Kingston, Ontario, Canada and [2]Department of Obstetrics and Gynecology, Kingston General Hospital, Kingston, Ontario, Canada.

Introduction: Pre-eclampsia (PE) is a disease affecting 5-8% of pregnancies worldwide. Women who smoke have a significantly decreased risk of PE, which may be due to an increase in carbon monoxide (CO) concentration in the blood, up to 14% carboxyhemoglobin (COHb). Menadione has been shown to increase CO production in perfused human placentas. Thus, the use of menadione as a method of raising tissue and blood CO in female mice was investigated. Methods: Female CD-1 mice (Charles River, USA) were given 1.5 g/L menadione sodium bisulfite (MSB) (Sigma-Aldrich, Oakville) in drinking water for seven days. Water was provided *ad libitum* and measured as average daily water intake per gram of body weight (mL/24 hr:g). %COHb and tissue CO levels in the spleen, kidney and liver were measured using gas chromatography (GC). Results: No significant increases in %COHb or taste aversion were observed in treated mice compared to the control. However, there was an increase in CO in the tissues of treated mice, with a significantly higher CO content in the kidneys of treated mice ($p<0.05$). Conclusion: 1.5 g/L MSB is a safe dose for use in non-pregnant female mice. Going forward, the dose of MSB will be increased within a tolerable range to attain the desired 5-10 %COHb level, and may hold promise as a method of CO delivery in pregnant mice. Supporting Agency: CIHR

81. CORM-A1 TREATMENT LEADS TO INCREASED BLOOD CARBOXYHEMOGLOBIN IN PREGNANT CD-1 MICE.
Karalyn E McRae[1], Nichole Peterson[1] and Graeme N Smith[1,2]. [1]Department of Biomedical and Molecular Sciences, Queen's University, Kingston, Ontario, Canada and [2]Department of Obstetrics and Gynecology,

Kingston General Hospital, Kingston, Ontario, Canada.

Introduction: Pre-eclampsia (PE) is a disorder affecting 5% of pregnancies, characterized by hypertension and proteinuria. While the etiology of PE is unknown, it is widely accepted that it is a result of impaired placental perfusion, which results in hypoxia in the placenta. CORM-A1 can be delivered to pregnant mice to increase blood carboxyhemoglobin (%COHb) levels. **Objectives**: This study aims to a) Quantify the increase in CO in blood %COHb following intermittent dosing with CORM-A1, at various concentrations, in pregnant mice, b) Determine fetal, litter and histological effect of CORM-A1. **Study Methods:** Female CD-1 mice were mated. Dams were treated with doses of CORM-A1 (Sigma Aldrich, USA) by IP injection on E10.5. %COHb was measured using gas chromatograph CO analyzer. Data are presented as mean±SD. Analysis was performed by Kruskal-Wallis test with Dunn's multiple comparison test. **Results:** Blood %COHb increased from 0.67%±0.10% at baseline (n=5) to 3.48%±0.67% at 15min post-CORM-A1 treatment (5mg/kg dose)(n=4). At 10mg/kg, %COHb is elevated at 15 and 30min to 3.95%±0.73% (n=6) and 3.05%±0.20% (n=6) respectively. There was no difference between treatment groups in maternal gestational weight gain, fetal or placental weight, or fetal outcomes at E17.5. **Conclusions:** Doses of 5, 8 and 10mg/kg CORM-A1 delivered by IP injection significantly increases %COHb from baseline at 15 minutes post-treatment. CORM-A1 may be a potential therapeutic for delivery of CO during pregnancy complicated by PE. **Funding:** CIHR Catalyst Grant (GNS), Ontario Graduate Scholarship (KM).