MITO2019

NOVEMBER 08 - 09 2019

Courtyard by Marriott Toronto Downtown

The 2nd Annual Conference of The Canada Mitochondrial Network and MitoCanada Foundation

DAY 1 - NOVEMBER 8, 2019

Patient Engagement in Research Keynote Address

Dr. Erin Walker

Patient Insight and Involvement Lead, UCL Partners

Originally hailing from Canada, Dr Erin Walker is currently based at an Academic Health Science Network, UCLPartners, in London, UK as the Patient Insight and Involvement Lead. She did her BSc (Hons) at the University of Victoria in Canada, before moving to the UK for a Master's degree in Psychology Research. She completed a PhD in Psychology in 2011 on quality of life for liver transplant patients at the University of Sheffield. She has worked on research projects involving adults post-stroke (King's College London), adults with Inflammatory Bowel Disease (King's College Hospital NHS Foundation Trust), and children and young people waiting for, or who have received, a heart and/or lung transplant (Great Ormond Street Hospital for Children NHS Foundation Trust). Dr Walker has spent the past 6 years focused on patient and public involvement and engagement (PPIE), first at the National Institute of Health Research (NIHR) Biomedical Research Centre (BRC) at Great Ormond Street Hospital, then at the NIHR University College London Hospitals BRC. Dr Walker has been a co-investigator on 4 grants from the NIHR, three as the lead for PPIE, and one as a patient representative. Dr Walker is also currently the PPIE co-investigator on the NIHR Children and Families Policy Research Unit, for the UK Department of Health and Social Care. Her research interest is in the area of involving children and young people with various mental and physical conditions in research.

Mitochondrial Diagnosis and Care Talks

Dr. Ingrid Tein, MD (Chair)

Associate Professor, Pediatrics, Laboratory Medicine and Pathobiology, University of Toronto

Senior Associate Scientist, Genetics and Genomic Biology Program, Research Institute at the Hospital for Sick Children, Toronto

Dr. Tein directs the Neurometabolic Clinic for the investigation and treatment of children with fatty acid oxidation, mitochondrial, and peroxisomal disorders and cofactor-responsive epilepsies and the ergometric investigation of metabolic myopathies using BOLD-MRI and 31P-MRS spectroscopy. The development of in vitro disease models to understand the underlying pathophysiological mechanisms in order to develop new therapies. She has identified novel clinical and biochemical phenotypes and genotypes, developed new diagnostic screening tests, and developed novel treatment strategies aimed at bypassing or correcting specific metabolic block which have decreased long-term morbidity and mortality in affected children and been implemented internationally. Her research has been supported by the Medical Research Council of Canada, Canadian Institutes of Health Research, Heart and Stroke Foundation, Muscular Dystrophy Association, United Mitochondrial Diseases Foundation and Rare Diseases Foundation.

Prof. Shamima Rahman

Professor of Paediatric Metabolic Medicine, UCL Great Ormond Street Hospital, London

Professor Shamima Rahman is Professor of Paediatric Metabolic Medicine at the UCL Great Ormond Street Institute of Child Health (ICH), and honorary consultant at Great Ormond Street Hospital for Children, London. She trained in Medicine at Oxford University, and in Paediatric Metabolic Medicine at Great Ormond Street Hospital. Professor Rahman established the Mitochondrial Research Group at ICH in 2000, with a mission to improve the diagnosis and outcomes for children affected by mitochondrial and other rare metabolic diseases. Her group focusses on discovering mitochondrial disease genes, developing novel computational diagnostic strategies, and investigating therapeutic approaches where there are currently no disease-modifying treatments.

Professor Rahman is an Editor of the Journal of Inherited Metabolic Disease and a Senior Editor of the Annals of Human Genetics. She has a passion for education and is currently Senior Adviser to the Society for the Study of Inborn Errors of Metabolism's Education and Training Advisory Committee. Professor Rahman sits on the Scientific Advisory Board of the French Muscular Dystrophy Association (AFM-Telethon), the Australian Mitochondrial Disease Foundation's Clinical and Scientific Review Panel,

and the Medical Advisory Boards of the Lily Foundation and the Freya Foundation, and acts as a special adviser to the Human Fertilisation and Embryology Authority.

Overview of Talk:

Mitochondrial disorders are notorious mimics long recognised to present with any combination of symptoms affecting one or multiple organs at any age, from intrauterine life to late adulthood. This phenotypic heterogeneity, coupled with the biochemical and genetic complexity of mitochondria (dynamic organelles with myriad roles in energy production, intermediary metabolism and cell signalling), leads to enormous diagnostic challenges. Next generation sequencing has introduced unparalleled opportunities for enhanced diagnosis of mitochondrial disease and led to the discovery of new disease genes at an astonishing rate. However, genome-wide sequencing approaches have also revealed that mitochondrial dysfunction may in many cases be secondary to non-primary mitochondrial genetic defects, adding further complexity to this field of medicine.

Dr. Amel Karaa

Director, Mitochondrial Disease Program

Assistant Professor, Harvard Medical School

Dr. Amel Karaa is a board certified internist and clinical geneticist, director of the mitochondrial disease program at the Massachusetts General Hospital in Boston. She received the 2013 United Mitochondrial Disease Foundation (UMDF) Fellowship and is conducting clinical research and clinical trials for mitochondrial disease. She was recently elected president of the Mitochondrial medicine Society and sits on the scientific and medical board for MitoAction and the UMDF. Dr. Karaa is also on the board of Rare New England and the newly launched Mitochondrial Care Network. She is committed to being an advocate for her mitochondrial disease patients and their families and to educate adult providers in recognizing and treating mitochondrial patients within the community.

Overview of Talk:

The mitochondrial medicine society (MMS) has previously highlighted the clinical landscape and physician practice patterns of mitochondrial medicine in the US and developed consensus criteria for diagnosis and management to improve patient coordinated care. In collaboration with US-based patient advocacy groups, a clinical care network was created to provide unified medical care to individuals with mitochondrial disease. The scope is to define, design and implement best practices in mitochondrial medicine to improve patients' clinical outcomes.

Mitochondrial Replacement Therapy Panel

Dr. Tania Bubela (Chair)

Co-Scientific Director, mitoNET

Dean, Faculty of Health Sciences, Simon Fraser University

Dr. Bubela was appointed Dean of the Faculty of Health Sciences at Simon Fraser University in September 2017. Prior to that appointment, she was Professor and Associate Dean (Research) in the School of Public Health and Adjunct Professor in Alberta Business at the University of Alberta (UofA), Canada. She joined the faculty of the UofA in 2004 after clerking for The Honourable Louise Arbour at the Supreme Court of Canada, articling at Field Law LLP in Edmonton, and being called to the bar (Law Society of Alberta) in 2005. Her research program in intellectual property and health law, focused on translational biomedical research, brings together her legal training and a PhD in biology and expertise in genetics and molecular biology. Her research program focuses on large collaborative science networks in genomics, gene therapy, and stem cell biology. It addresses barriers to the development and effective translation of new technologies.

Dr. Vardit Ravitsky

Associate Professor, Université de Montréal

Dr. Ravitsky is an elected Board member and Treasurer of the International Association of Bioethics (IAB). She is a member of CIHR's Institute Advisory Board on Research Excellence, Policy and Ethics. Previously, she was a Board Member and Ethics Designate of CIHR's Institute of Genetics (IG) and Co-Charired this Institute's "GE3LS and Health Services and Policy Research Priority and Planning Committee" (GE3LS stands for Genomics research and its Ethical, Economic, Environmental, Legal, and Social aspects). Dr. Ravitsky is a member of the University of Montreal's Public Health Research Institute (IRSPUM), of the Quebec Reproduction Network (RQR), and of the Canadian Fertility and Andrology Society (CFAS). Previously, she was faculty at the Department of Medical Ethics, School of Medicine, at the University of Pennsylvania. She was also a Senior Policy Advisor at CIHR's Ethics Office and a GE3LS consultant to Genome Canada.

Prof. Ravitsky's research focuses on reproductive ethics and the ethics of genetic and genomics research. Her research interests in bioethics also include research ethics, health policy and cultural perspectives. She is particularly interested in the various ways in which cultural frameworks shape public debate and public policy in the area of bioethics. Her research projects are funded by CIHR, FRQSC, SSHRC, and Genome Canada. She published over 100 articles, book chapters and commentaries on bioethical issues, and is lead-editor of "The Penn Center Guide to Bioethics".

Overview of Talk:

Mitochondrial Replacement Therapy: how language shapes the policy debate

Canada, like other countries, currently bans Mitochondrial Replacement Therapy (MRT) and even research that could advance our ability to perform it. I argue that this ban is misguided, as it impedes the future access of Canadians to a potential prevention strategy that would allow individuals with mitochondrial disease to have unaffected genetically related children. I will further argue that the public/policy debate surrounding MRT has been influenced by oft-sensationalist language used in media and scientific reporting, portraying it as creating "three-parent babies" or even "genetically-modified children". I will call for a responsible use of terminology to enhance informed policy approaches.

Dr. Alice Virani

Director, Clinical Ethics Service, Provincial Health Services Authority of BC

Clinical Assistant Professor, Dept. of Medical Genetics, UBC

Dr. Alice Virani is the Director of the Clinical Ethics Service for the Provincial Health Service Authority of BC. She is a Clinical Assistant Professor in the Department of Medical Genetics at UBC. She enjoys teaches ethics in a number of graduate, clinical and public settings. Alice has also spent 9 years serving as the ethicist on a number of different research ethics boards. Her research interests relate to the many ethical issues inherent within clinical practice and research in genetic and genomic medicine and she has published in a broad range of peer reviewed journals and lay media in this area.

Before moving into ethics, Alice was a genetic counselor in the Division of Maternal Fetal Medicine at Columbia Presbyterian Hospital in New York. She has a master's in human sciences from Oxford University, a masters in Genetic Counseling from Sarah Lawrence College, a master's in public health from Columbia University, and a PhD in Genetics and Ethics from UBC. Alice also does consulting work for clients such as the Canadian Institute of Health Research, the Public Health Agency of Canada and Health Canada.

Overview of Talk:

Ethical Considerations of MRT Therapy

This presentation will focus on the various ethical considerations that arise when discussing MRT therapy in relation to both research and clinical applications. Principles and values related to autonomy and consent, reproductive freedoms and parental responsibilities as well as risks on an individual and societal level will be examined. Finally, ethical governance mechanisms that include transparency and robust stakeholder engagement will be explored.

Ms. Naomi Laliberte

Patient Advocate

Naomi Laliberte is a mitochondrial disease patient who works as a dental hygienist in Montreal. She was diagnosed at the age of 31 when her children fell ill. As she continues to care and advocate for herself, 2 children and family members, she focuses her efforts on helping families navigate the diagnostic process.

Parallel Symposium: Mitochondrial Function and assessment in brain developmental illnesses

Dr. Martin Beaulieu (Chair)

Associate Professor, Department of Pharmacology and Toxicology, University of Toronto

Canada Research Chair (Tier 1) in Molecular Psychiatry

Dr Beaulieu received a Ph.D. in Neurological Sciences from McGill University and completed his post-doctoral training at Duke University. Prior to his recruitment to the University of Toronto, Dr. Beaulieu was an associate professor and Canada Research Chair (Tier 2) in the Department of Psychiatry and Neuroscience at Laval University. Dr. Beaulieu's research is aimed at understanding how cellular and molecular mechanisms regulated by psychoactive drugs intersect with genetic risk factors for mental illnesses such as schizophrenia, depression and bipolar disorder. Dr. Beaulieu has pioneered work establishing a role for Beta-arrestin signaling in the brain in vivo and has established its importance in D2 dopamine receptors (D2R) functions.

Dr. Ruth Slack

Professor, University of Ottawa Dept. of Cellular and Molecular Medicine

Director, University of Ottawa Brain and Mind Research Institute

Dr. Slack is a full professor at the University of Ottawa in the Department of Cellular and Molecular Medicine, and has served as Vice-Dean, Research since July 2017. She is a Reviewing Editor for the Journal of Neuroscience. She has served on several review panels including CIHR, CFI, Ontario Mental

Health Foundation, HSFO, Alberta Heritage Foundation, and the Retinitis Pigmentosa Research Foundation. She is a Fellow of the Royal Society of Canada.

Dr. Anne Bassett

Clinician Scientist, Campbell Family Mental Health Research Institute, CAMH

Professor, Department of Psychiatry, University of Toronto

Dr. Anne Bassett heads the Clinical Genetics Research Program and is a Clinician Scientist in the Campbell Family Mental Health Research Institute at CAMH. She is also a Senior Scientist at the Toronto General Research Institute, holds the Dalglish Chair at the University Health Network, and is Professor of Psychiatry at the University of Toronto. She is an Associate Member of the Canadian College of Medical Geneticists. She is a Senior Scientist at the Toronto General Research Institute Dr. Bassett is the author of more than 170 peer-reviewed articles, other papers, and book chapters. Dr. Bassett is an internationally renowned expert in the genetics of complex developmental disorders, especially schizophrenia and serious congenital cardiac disease (blue babies), as well as 22q11.2 deletion syndrome and other disorders associated with major structural changes in the human genome.

Dr. Angela Scott

Assistant Professor, Department of Pathology and Molecular Medicine, McMaster University

Dr. Angela Scott is a neurophysiologist with a wide range of research training and expertise in the dynamic molecular and cellular relationships that govern development and neuroplasticity within the nervous system. Following the completion of her Ph.D. at the University of British Columbia, she has worked as a postdoctoral fellow at the University of Edinburgh and McMaster University. Upon starting her faculty position in the Department of Pathology and Molecular Medicine at McMaster University in 2017, her research has focused on the inter- and intra-cellular relationships of astrocytes (glial cells) and neurons responsible for maladaptive changes that underlie neurological disorders.

Parallel Symposium: Brazilian Native Products – Potential alternatives for drug/supplement development against mitochondrial dysfunction

Dr. Alencar Kolinski Machado (Chair)

Graduate Program in Nanosciences, Franciscan University, Santa Maria, RS, Brazil

Bachelor in Biomedicine by the Franciscan University, Brazil (UFN – 2012). Master (UFSM – 2014) and PhD (UFSM – 2017) in Pharmacology by the Federal University of Santa Maria, Brazil. Part of the PhD was developed in the University of Toronto as a PhD exchange student (UofT - PDSE/CAPES – 2015). Currently working as Adjunct Professor at the Franciscan University – Brazil, and is member of the Nanoscience Graduate Program at the same University, developing researches involving mitochondrial dysfunction, oxidative stress, neuropharmacology, and natural products.

Dr. Francine Carla Cadoná

Graduate Program of Biosciences and Health, West University of Santa Catarina, Joaçaba, SC, Brazil

Graduate Program in Sciences of Health and Life, Franciscan University, Brazil

Biologist (2012), Master's (2013) and Ph.D. (2016) at Biochemistry from Federal University of Santa Maria. During her Ph.D., she conducted fellowship research in Universitat de Barcelona in Spain (2015). She has postdoc at University of Toronto (2018-2019). At the moment, she is Professor in Postgraduate Program in Health Sciences and Life at Franciscan University in Santa Maria (RS) and in Postgraduate Program in Biosciences and Health at University of West of Santa Catarina in Joaçaba (SC). She develops studies in the area of nutrigenetic and nutrigenomics, focus on antitumor natural products. She has experience in Biochemistry, Molecular Biology, Genetics and Cell Culture.

Prof. Mirian Salvador

Graduate Program in Biotechnology, University of Caxias do Sul, Caxias do Sul, RS, Brazil

Graduated in Pharmacy by the Federal University of Rio Grande do Sul (1981), Specialist in Biotechnology by University of Caxias do Sul and PhD in Chemistry by Universidad de La Republica del Uruguay, Montevideo (1995). She is currently a full professor at the University.

Parallel Symposium: Advocating for Care and Preparing for Meeting with Clinicians

Dr. Mark Tarnopolsky, MD

Professor, Division of Neurology, Departments of Pediatrics and Medicine, McMaster University

Clinical & Research Director, Corkins/Lammert Family Neuromuscular and Neurometabolic Clinic, McMaster University

Dr. Tarnopolsky's research focuses on nutritional, exercise, pharmacological and genetic therapies for neurometabolic (primarily mitochondrial), neuromuscular, and neurogenetic disorders as well as diseases associated with aging. He has authored or coauthored more than 400 scientific articles. He has also lectured widely in the area of neurology (neuromuscular and neurometabolic disorders), aging, and physiology. He has served on several editorial and scientific boards (UMDF, MSSE, Mitochondrion, PLOS ONE, Barth Foundation) and has been on Grant Selection Committees for NSERC (Animal Biology, 2003-2006, Chair, 2006), CIHR Biology of aging Committee (2006), CIHR Movement Committee (2012, 2013, 2015), Chair of the Emerging Team Grant: Mobility in Aging (2007) and a member of the phase I CIHR Foundation grant committee (2017). He is the founder (2015), and current CEO and CSO of Exerkine Corporation.

Dr. Ingrid Tein, MD

Associate Professor, Pediatrics, Laboratory Medicine and Pathobiology, University of Toronto

Senior Associate Scientist, Genetics and Genomic Biology Program, Research Institute at the Hospital for Sick Children, Toronto

Dr. Tein directs the Neurometabolic Clinic for the investigation and treatment of children with fatty acid oxidation, mitochondrial, and peroxisomal disorders and cofactor-responsive epilepsies and the ergometric investigation of metabolic myopathies using BOLD-MRI and 31P-MRS spectroscopy. The development of in vitro disease models to understand the underlying pathophysiological mechanisms in order to develop new therapies. She has identified novel clinical and biochemical phenotypes and genotypes, developed new diagnostic screening tests, and developed novel treatment strategies aimed at bypassing or correcting specific metabolic block which have decreased long-term morbidity and mortality in affected children and been implemented internationally. Her research has been supported by the Medical Research Council of Canada, Canadian Institutes of Health Research, Heart and Stroke Foundation, Muscular Dystrophy Association, United Mitochondrial Diseases Foundation and Rare Diseases Foundation.

Dr. Samantha Marin, MD

Assistant Professor of Pediatrics, Division of Child Neurology, Winnipeg, Manitoba

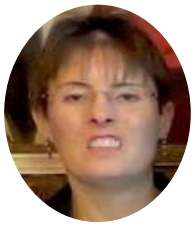
_Dr. Samantha Marin completed her medical training and Pediatric Neurology residency at McMaster University (Hamilton, Ontario). Subsequently, she pursued additional training in the form of an NIH-sponsored North American Mitochondrial Disease Consortium (NAMDC) Fellowship located in multiple sites across the U.S.A with expertise in mitochondrial disease (Seattle, WA; San Diego, CA; Houston, TX). In 2015, she started as a clinician and Assistant Professor of Pediatrics, Division of Child Neurology in Winnipeg, Manitoba. Her clinical & research Interests include mitochondrial disease, neuro-genetics, neuro-metabolics, and demyelination.

Family/ Patient Panelists

Ms. Naomi Laliberte

Patient Advocate

Naomi Laliberte is a mitochondrial disease patient who works as a dental hygienist in Montreal. She was diagnosed at the age of 31 when her children fell ill. As she continues to care and advocate for herself, 2 children and family members, she focuses her efforts on helping families navigate the diagnostic process.



Lisa Krupa

MitoCanada Patient & Family Advisory Committee

Lisa is a Mitochondrial Myopathy patient who has been symptomatic since infancy, and a ventilator + feeding tube user since 2007. She earned an HBSc in Applied Bio-Molecular Science, and an HBA in Psychology from Lakehead University, before going on to pursue an MD at the American University of the Caribbean. Unfortunately, the tropical climate led to a dramatic worsening of mitochondrial disease symptoms, forcing her withdrawal from medical school in second-year.

She lives in Thunder Bay, Ontario, independently managing her daily medical needs in a wheelchair-friendly house she helped design, with a bathroom & kitchen also adapted for upper-body weakness. A love of good food has also led her to make a specialty of dysphagia-friendly recipes and food-preparation techniques.

Sharlene McKeown, *Patient Advocate*

Mitochondrial Transplant Fireside Chat

Overview: In this fireside presentation Dr.s Emani and McCully will share their studies using a novel therapy for cardioprotection based on mitochondrial transplantation. This approach uses replacement of native mitochondria damaged by ischemia/reperfusion injury with viable, respiration-competent mitochondria isolated from non-ischemic skeletal muscle tissue, obtained from the patient's own body. Dr. McCully will provide results and insight from large animal ischemia/ reperfusion studies. Dr. Emani will provide data from a pilot mitochondrial transplantation human clinical trial in pediatric patients having ischemia/reperfusion injury and requiring extracorporeal membrane oxygenation support, and provides steps moving forward.

Dr. Ana Andreazza

mitoNET Founder, Scientific Director

Canada Research Chair (Tier II) in Molecular Pharmacology of Mood Disorders

Dr. Andreazza is an Associate Professor in the Departments of Pharmacology & Toxicology and Psychiatry and holds a holding Tier II Canada Research Chair in Molecular Pharmacology of Mood Disorders. She is cross-appointed as a collaborator Scientist at the Centre for Addiction and Mental Health. Her research focuses on the understanding of the role of redox modulations and mitochondrial dysfunction in mental illness, especially in mood disorders. Dr. Andreazza's current research focus is on the brain and its redox biology, with particular reference to the role of mitochondrial dysfunction and the impact of redox modification on the inflammatory system and illness progression in major psychiatric disorders and mitochondrial diseases, with the objective of identifying biological targets that will open doors to the development of new treatment strategies.

Dr. James McCully, MD

Associate Professor of Surgery, Harvard Medical School and Boston Children Hospital

Dr. McCully's research focuses on the mechanisms and subcellular localization of the biochemical and molecular events contributing to myocardial cell death. In particular, his lab has

investigated the discriminant and/or coordinate mechanisms leading to ischemia/reperfusion injury in the neonate, child, mature and aged male and female with particular emphasis on the development of novel and specific cardioprotective protocols.

Recently he has developed a novel approach to cardioprotection using autologous mitochondrial transplantation. His research has demonstrated that transplantation of autogeneic mitochondria into the ischemic zone of the myocardium during early reperfusion significantly enhances post-ischemic functional recovery. These studies have shown that the transplanted mitochondria act externally and then are internalized by myocardial cells to provide myocellular rescue and cardioprotection. The transplanted mitochondria upregulate cytokines associated with enhanced post-infarct cardiac function and improvement of cardiac remodeling and upregulate protein pathways associated with the generation of precursor metabolites for energy and cellular respiration with no immune or auto-immune response. The transplanted mitochondria are internalized through actin-dependent endocytosis and rescue cell function by increasing ATP content and oxygen consumption rate. Significantly, he has demonstrated that internalized mitochondria replace depleted or damaged mitochondrial (mt) DNA.

Dr. Sitaram Emani, MD

Associate Professor of Surgery, Harvard Medical School & Boston Children Hospital

Following completion of training in adult cardiothoracic surgery and pediatric cardiothoracic surgery, Dr. Emani joined the staff at Boston Children's Hospital. Dr. Emani is the surgical director for the complex biventricular repair program, and adult congenital heart program. His clinical expertise also includes valve repair and replacement strategies, neonatal heart surgery, and minimally invasive surgery for children. His research efforts include strategies to "grow" a left heart – including stem cell therapy - in patients with borderline left heart who otherwise would undergo single ventricle palliation. A major problem in children with heart valve disease is the lack of a valve that can grow as a child grows. This motivated him to pursue a design of expandable valve technologies, to reduce the need for reoperation in children. Additional research interests include use of 3-D printing for surgical planning and understanding the clotting system in children after heart surgery.

DAY 2 - NOVEMBER 9, 2019

Neuro-ophthalmology and Mitochondrial Disease Talk

Dr. Rustum Karanjia. MD

Assistant Professor, Vice Chair (Research), University of Ottawa

Junior Clinical Research Chair Fellowship for Ophthalmology

Bio: Dr. Karanjia is a Neuro-ophthalmologist at the University of Ottawa Eye Institute. Having completed his medical training and PhD in Canada, he completed a fellowship at UCLA with Dr. Alfredo A. Sadun, a world's expert on LHON. He is actively involved in clinical trials on LHON and is a Board member for the International Foundation on Optic Nerve Disease. He has a number of peer-reviewed publication on LHON and is active in the community, having spoken at the LHON Day at the United Mitochondrial Disease Foundation annual symposium on several occasions. Dr. Karanjia obtained both his PhD and MD from Queen's University and completed his residency in Ophthalmology at the University of Ottawa. He is currently an Assistant Professor and Vice-Chair (Research) at the University of Ottawa and holds the Jr. Clinical Research Chair Fellowship for Ophthalmology.

Big Data and Informatics in Research Symposium

Dr. Ken Evans (Moderator)

President, Indoc Research

Dr Evans is President of Indoc Research, a not-for-profit company that helps medical researchers manage, share and analyze complex clinical, molecular and imaging data. Indoc-built platforms support a variety of research needs, including the Ontario Brain Institute's large scale brain research programs (Brain-CODE: https://www.braincode.ca/). Dr Evans spent 15 years in the pharmaceutical and biotech industries, during which time he led the global clinical development of a number of innovative drugs. Dr. Evans has been instrumental in the start-up and implementation of several major collaborative (industry/academia) research initiatives, including projects aimed at improving clinical assessments (Parkinson's, Huntington's disease, Major Depressive Disorder) and at predicting drug/placebo response. Dr. Evans has also been involved in a number of translational biomarker research projects, including the use of PET imaging to predict drug response and various proteomic and genomic biomarker discovery and development programs in various diseases, including

cancer and depression. Dr Evans holds two adjunct appointments: Associate Professor in the Department of Pathology and Molecular Medicine at Queen's University, and Lecturer in the Department of Psychiatry at the University of Toronto.

Dr. Mojib Javadi

Director, Program Development & Research Operations, Indoc Research

Mojib Javadi holds the position of Associate Director, Program Development at Indoc Research since 2014. At Indoc Research, Mojib works with investigators from partner organizations to develop provincial and federal grants for new data management and informatics technologies and solutions. He is the project manager for funded collaborative projects with partner academic groups and focuses on the implementation of molecular data management strategy and functions. Mojib holds a Ph.D. in Molecular Cancer Biology from the University of Toronto.

His doctoral work focused on hematopoiesis and myeloid leukemias. Mojib was funded by NSERC for an industry post-doctoral fellowship with Lorus Therapeutics where he developed small molecular kinase inhibitors targeting solid tumors. Mojib was the Management Fellow at Ontario Brain Institute, working on data standardization efforts and developing potential informatics sustainability models.

Trudo Lemmens

CandJur, LicJur (KULeuven), LLM *bioethics*, DCL (McGill)

Professor and Scholl Chair in Health Law and Policy, University of Toronto

Trudo Lemmens is a Professor and Scholl Chair in Health Law and Policy. He is cross appointed to the Dalla Lana School of Public Health, the Faculty of Medicine, and the Joint Centre for Bioethics. His research focuses on the interaction between law, governance tools, and ethical norms and values in the context of health care, biomedical research, pharmaceutical and other health product development, and knowledge production.

Since joining the Faculty of Law, Professor Lemmens has been a member of the School of Social Science of the Institute for Advanced Study in Princeton, a visiting fellow of the Royal Flemish Academy of Belgium for Science and the Arts, a visiting professor at the University Torcuato di Tella (Buenos Aires, Argentina), the University of Otago (Dunedin, New Zealand), the Pontificia Universidad Javeriana (Bogota, Colombia) and the K.U.Leuven (Belgium); a Plumer Visiting Fellow at Oxford's St. Anne's College, and an academic visitor at the Faculty of Law and the HeLEX Center for Health, Law and Emerging Technologies of the University of Oxford. Professor Lemmens' publications include the co-authored book Reading the Future? Legal and Ethical Challenges of Predictive Genetic Testing, the co-

edited volumes Regulating Creation: The Law, Policy and Ethics of Assisted Human Reproduction, and Law and Ethics in Biomedical Research: Regulation, Conflict of Interest, and Liability, as well as numerous chapters and articles in national and international law, policy, science, medicine and bioethics journals. He is currently a member of the Advisory Committee on Health Research of the Pan American Health Organization. In the last five years, he was a member of two expert panels of the Council of Canadian Academies: one on access to health data, the other on advance requests and medical assistance in dying.

Overview of Talk:

Data Transparency and Privacy in the Context of Rare Diseases

Data transparency is increasingly recognized as a key tool to strengthen the integrity of biomedical research, but also as a tool to promote innovation. Health Canada has taken bold steps to promote transparency by creating a presumption that data submitted in the context of drug approval will be shared. Various professional initiatives, particularly in the context of genomics, are also emphasizing the importance of data sharing. Yet, concerns have been expressed with respect to health information privacy of those participating in research. This presentation will discuss the rationale for data transparency, some recent initiatives and developments, and explore concerns about privacy, particularly in the context of rare diseases.

Adrian Thorogood

Lawyer and Academic Associate, McGill University

Adrian (B.A.&Sc., B.C.L.&LL.B., LL.M.) is a lawyer and Academic Associate at the Centre of Genomics and Policy (CGP) at McGill University. His legal research focuses on how genomic sequencing platforms, information and networking technologies, open science practices, and patient empowerment movements are disrupting biomedical research and health care. He has published numerous articles on health data governance and regulation, the duties and liabilities of health professionals, and the privacy of health information. He is also the Regulatory and Ethics Manager of the Global Alliance for Genomics and Health, a public-private consortium that develops standards for genomic data exchange. In this position, he coordinates the development of policy frameworks addressing consent, privacy and security, and research oversight enabling responsible data sharing between countries, institutions, and sectors.

Overview of Talk:

Going Big Means Going Global: Navigating Legal Variation in Collaborative Health Research.

Health research is increasingly characterized by Big Data approaches. Researchers seek to collect a massive volume and variety of data from large cohorts, in order to discern new patterns about health and disease. But no researcher, institution, or even country has sufficient data to act alone. International data sharing is therefore essential to achieve the promise of Big Data in health research. Through innovative governance and network technologies, international collaborations can successfully navigate diverse legal frameworks and advance the standard of care for patients everywhere.

Dr. Geoff Anderson, MD

Professor, Institute of Health Policy, Management and Evaluation, University of Toronto

Geoff Anderson is currently an adjunct scientist at ICES and a professor at the Institute of Health Policy, Management and Evaluation, University of Toronto, where he holds the Chair in Health Management Strategies. Dr. Anderson completed his undergraduate training at Carleton University and his medical training at the University of Ottawa. After interning at the Ottawa Civic Hospital, he was awarded a National Health Fellowship and completed an M.Sc. in Community Medicine (Health Administration) at the University of Toronto. He was then awarded an Ontario Postgraduate Fellowship and a Pew Foundation Health Policy Fellowship and completed a Ph.D. in Health Policy Analysis at RAND in 1988. Prior to moving to Toronto, Dr. Anderson held academic appointments at the University of Ottawa and the University of British Columbia.

Overview of Talk:

Protecting Data Privacy: Approaches to Analyze Sensitive Data in a Secure Environment to Protect Data Privacy

Bringing together diverse streams of patient-generated data - biological, personal and health outcome - in a high-performance computing environment where they are accessed by teams of researchers and data scientists is a key tool for 21st century discovery research. However, the use of these patient-generated data comes with a set of societal and individual expectations around privacy and data security. To address these issues our team has utilized a "Restricted Data Environment" or "RDEN" that enables researchers to conduct complex analyses while in a secure, remotely accessible environment that reduces the risk of breach or re-identification. This talk discusses our experience with the RDEN in the context of two existing research initiatives link biological, personal and health outcome data.

Parallel Symposium: Age, Muscle, Exercise and Mitochondria

Dr. David Hood (Chair)

Professor, School of Kinesiology and Health Science, Faculty of Health, York University

Canada Research Chair (Tier 1) in Cell Physiology

Director, Muscle Health Research Centre

Dr. Hood's research is focused on Mitochondrial Biogenesis and Turnover in Health and Disease specifically in mammalian skeletal and cardiac muscles utilizing mouse and rat models as well as cell culture. Common experimental models used within the lab include 1) chronic exercise, brought about running, or by electrical stimulation in vivo and in cell culture, 2) muscle disuse, usually produced by denervation, and 3) aging. Physiological, biochemical and molecular biology techniques are employed to study mitochondrial turnover in these tissues.

Overview of Talk:

Mitochondrial turnover in muscle: effect of age and exercise

In skeletal muscles, mitochondrial metabolism is increased during exercise, to provide the energy required for locomotion and physical activity. Repeated bouts of exercise lead to an adaptive increase in mitochondrial content, to provide a higher capacity for energy supply and a more efficient oxidation of fats. These changes ensure better long-term performance without undue fatigue. With age, muscle mitochondria lose some of their abilities to generate energy, and they also produce harmful reactive oxygen species in greater abundance. The reason for this is that the synthesis of new, healthy mitochondria is not activated as highly in aged muscle, and aged muscle is also less able to remove dysfunctional mitochondria as they arise. However, exercise can stimulate healthy mitochondrial production, and activate the efficient removal of old mitochondria, to help restore muscle health as we age.

Dr. Mark Tarnopolsky, MD

Professor, Division of Neurology, Departments of Pediatrics and Medicine, McMaster University

Clinical & Research Director, Corkins/Lammert Family Neuromuscular and Neurometabolic Clinic, McMaster University

Dr. Tarnopolsky's research focuses on nutritional, exercise, pharmacological and genetic therapies for neurometabolic (primarily mitochondrial), neuromuscular, and neurogenetic disorders as well as diseases associated with aging. He has authored or coauthored more than 400 scientific articles. He has also lectured widely in the area of neurology (neuromuscular and neurometabolic disorders), aging, and physiology. He has served on several editorial and scientific boards (UMDF, MSSE, Mitochondrion, PLOS ONE, Barth Foundation) and has been on Grant Selection Committees for NSERC (Animal Biology, 2003-2006, Chair, 2006), CIHR Biology of aging Committee (2006), CIHR Movement Committee (2012, 2013, 2015), Chair of the Emerging Team Grant: Mobility in Aging (2007) and a member of the phase I CIHR Foundation grant committee (2017). He is the founder (2015), and current CEO and CSO of Exerkine Corporation.

Overview of Talk:

Exercise and nutrition for older adults and those with mitochondrial myopathy

Older adults show many features of mitochondrial dysfunction also seen in patients with primary genetic mitochondrial myopathies including; lower enzyme activity, COX negative muscle fibres, mtDNA deletions, atrophy and lower oxygen consumption (VO2peak). Both endurance and resistance exercise training have been shown to improve important clinical metrics including; VO2peak, muscle strength, muscle endurance, higher mitochondrial enzyme activity and improvements in functional capacity. Some of the aforementioned benefits can be enhanced in older adults with multi-nutrient supplements (milk protein, calcium, vitamin D, fish oil and creatine monohydrate). Similar training programs have been used in patients with mtDNA point mutations and mtDNA deletions with similar improvements in VO2peak, muscle strength and no evidence of deleterious effects. It is likely that multi-nutrient supplements as described herein would further enhance these gains but they have not yet been evaluated in this group. The combination of creatine monohydrate + coenzyme Q10 + alpha lipoid acid + vitamin E was found to lower oxidative stress markers and lactate in mitochondrial myopathy patients but the long term outcomes, especially with co-prescribed exercise has not yet been evaluated.

Dr. Graham Holloway

Associate Professor, Human Health and Nutritional Sciences, University of Guelph

My research is primarily focused on understanding the regulation of mitochondrial bioenergetics, with a particular interest in studying fatty acid oxidation (breakdown of fat yielding energy) in skeletal and cardiac muscle. I use a variety of techniques to examine mitochondrial function (isolated mitochondria, permeabilized fibres, whole muscle incubations), use molecular biological approaches to up-and down-regulate mitochondrial proteins, as well exercise, altered nutrition and aerobic training to study novel regulation in mitochondrial bioenergetics. We apply basic knowledge garnered from these studies to the study of human exercise performance as well as type 2 diabetes, heart failure, diabetic cardiomyopathy and various neuropathologies, conditions that

have all been affiliated with alterations in mitochondria as a key event in the progression and/or development of the disease.

Overview of Talk:

Mitochondrial ADP sensitivity: Implications to redox balance and aging

While the aetiology of sarcopenia is poorly defined, and likely involves a complex interaction of a variety of mechanisms, alterations in mitochondrial function, and in particular an increase in reactive oxygen species (ROS), have been implicated as an underlying cause. It is our working hypothesis that the transport of ADP into the mitochondrial matrix is decreased with aging, increasing mitochondrial ROS, contributing to age-associated redox stress. Importantly, mitochondrial ADP sensitivity appears to respond to exercise and dietary interventions, raising the potential for this key parameter to be targeted in future preventative approaches.

Parallel Symposium: Mitochondrial Function and Disease

Dr. Jason Maynes, MD

Hospital for Sick Children, Toronto

Adjunct Associate Professor of Biochemistry, University of Toronto

Associate Chief of Perioperative Services, Research Perioperative Services

The research in Dr. Maynes' lab focuses on three main areas that attempt to continue my clinical training in paediatrics and anaesthesia with my research training in biophysics: (1) the mechanism of anaesthetic action and anaesthetic off-targets, (2) proteins involved in mitochondrial dynamics and, (3) high-content imaging and image analysis. To study mitochondria and other cellular processes, Dr. Maynes employs high-content imaging. Unlike traditional confocal microscopy, we image thousands of cells at a time using 96-or 384-well plates and use automated image processing algorithms to determine specified metrics from every cell in every image. This removes the traditional bias associated with manual characterization of confocal images. He has developed machine learning algorithms that automatically identify, quantify, and then classify mitochondrial shape and function in a cell population of interest. He also extended these techniques to other disease phenotypes of relevance to paediatric anaesthestia including pulmonary stenosis, dilated cardiomyopathy and chemotherapy-induced cardiac dysfunction. Using custom assays, we are able to perform high-throughput drug screening to look for agents that attenuate or eliminate the disease phenotype observed.

Overview of Talk:

Targeting Mitochondrial Dysfunction in Heart Failure

The heart is a highly dynamic organ, with significant metabolic demands. As a result, alterations to mitochondrial function are both a symptom and a cause of heart failure. In the process of pediatric heart

failure, we have identified adverse changes to proteins that maintain mitochondrial quality and structure, promoting the formation of smaller, less efficient mitochondria and enhancing organelle degradation. This dual hit to the mitochondria (loss of quality and reduction in number) leads to inadequate energy production for the cardiomyocyte. The altered proteins represent novel targets to restore the energy balance that exists in heart failure.

Dr. Walid Houry

Professor, Departments of Biochemistry and Chemistry, University of Toronto

Dr. Walid A. Houry is Professor in the Department of Biochemistry and in the Department of Chemistry at the University of Toronto. Dr. Houry obtained his MSc (1991) and PhD (1996) from Cornell University and then did his postdoctoral training at the Sloan-Kettering Institute (1996-1997) in New York City and at the Max-Planck-Institute for Biochemistry (1997-2000) in Munich, Germany. He is interested in the general area of cellular stress responses and the role of molecular chaperones and ATP-dependent proteases in these responses. To this end, his group utilizes various structural, biophysical, biochemical, proteomic, and cell biological approaches to understand the mechanism of function of these chaperones and proteases. His group is also interested in the development of novel anticancers and antibiotics by identifying compounds that target these chaperones and proteases and result in the dysregulation of protein homeostasis in the cell.

His work has been recognized by several awards including Visiting Scientist of the National Research Foundation of South Africa, Tokyo Biochemical Research Foundation Award, Canada Foundation for Innovation Leaders Opportunity Fund, Canadian Institutes of Health Research New Investigator, and Premier's Research Excellence Award. Dr. Houry is currently an associate editor of Frontiers in Molecular Biosciences (2014-current) and on the Editorial board of Journal of Biological Chemistry (2017-2022) and Microbial Cell (2014-current).

Overview of Talk:

Dysregulation of Human Mitochondrial ClpP Protease Activity by Acyldepsipeptides Analogs Leads to Apoptotic Cell Death

Acyldepsipeptides (ADEPs) are potential novel antibiotics. They dysregulate the activity of the highly conserved tetradecameric bacterial ClpP protease leading to bacterial cell death. Here, we identified several ADEP analogs that are potent dysregulators of the human mitochondrial ClpP (HsClpP). These ADEPs interact tightly with HsClpP causing the protease to non-specifically degrade model substrates. Dysregulation of HsClpP activity by these ADEPs was found to have cytotoxic effects in multiple human cell lines as a result of the activation of the intrinsic, caspase-dependent apoptosis. ADEP-HsClpP co-crystal structure was solved for one of the analogs revealing a highly complementary binding interface formed by two HsClpP neighbouring subunits but, unexpectedly, with HsClpP in the compact conformation. Given that HsClpP is highly expressed in multiple cancers and has important roles in cell metastasis, our findings suggest a novel therapeutic potential for ADEPs in cancer treatment.

Dr. Larry Singh

Research Scientist, Center for Mitochondrial and Epigenomic Medicine, Children's Hospital of Philadelphia

Dr. Singh is a research scientist with CHOP's Center for Mitochondrial and Epigenomic Medicine where he is working on techniques for extracting off-target mitochondrial sequencing from next-generation sequencing (NGS) data. He has an extensive background in NGS with experience as a post-doctoral fellow with the University of Pennsylvania and research fellow with the National Human Genome Research Institute (NHGRI)/National Institutes of Health (NIH). Dr. Singh has worked with Illumina, 454 and Ion Torrent sequencing platforms in various applications including, whole exome sequencing, whole genome sequencing, RNA-seq, CHIP-seq and RIP-seq.

Overview of Talk:

Autism and mitochondria: a spectrum of possibilities

We investigated the association between mitochondrial DNA haplogroups and the risk of autism spectrum disorders (ASD). Using genetic data from 1624 patients with ASD and 2417 healthy parents and siblings from the Genetic Resource Exchange consortium, we found that individuals with European haplogroups I,J,K,O-X, T and U and Asian and Native American haplogroups A and M were at increased risk of ASD compared to the most common European haplogroup R0. These findings indicate that mitochondrial DNA haplogroups may contribute to the risk of ASD, and further suggest a role of mitochondrial dysfunction in ASD.

Dr. Rob Laister

Group Leader, Princess Margaret Cancer Centre, Toronto

Dr. Laister completed his doctoral training at the University of Toronto in the department of Medical Biophysics where he studied protein NMR spectroscopy and the DNA damage response in the laboratory of Dr. Cheryl Arrowsmith. As a post-doctoral fellow, Dr. Laister trained with Dr. Mark Minden where he worked on tumour cell metabolism and drug discovery in acute myeloid leukemia. He was also a member of Dr. Frank Sicheri's laboratory at the Samuel Lunenfeld Research Institute studying the structural biology of protein kinase complexes. Dr. Laister currently leads a research group at the Princess Margaret Cancer Centre that focuses on pre-clinical drug development for hematological malignancies. Two major themes to the group's current work include understanding how blood cancers adapt to conditions of nutrient stress and determining how metabolites communicate signals between the cellular components of the tumour microenvironment. Dr. Laister's group also collaborates with the lymphoma program at the Princess Margaret Cancer Centre and the CCTG Hematology group to

develop and implement clinical trial companion studies aimed at identifying and characterizing the function of proteomic and metabolic markers correlated with clinical outcomes (Lymphoma.ca)

Overview of Talk:

Targeting Glutamine Metabolism in Non-Hodgkin Lymphoma

Aggressive lymphomas require a constant flux of nutrients to feed and fuel the process of cellular growth. A number of classical onco-proteins have now been shown to regulate pathways associated with cellular metabolism and chief among them in the onco-protein MYC, the genetic dysregulation of which confers poor prognosis in NHL. MYC regulates multiple aspects of glutamine metabolism and we have profiled how glutamine is utilized via mitochondrial metabolism in lymphoma cells. Targeted inhibition of glutamine flux is toxic to lymphoma cells and compromises metabolic flux through the TCA cycle. Agents capable of creating a state of glutamine deficiency may be viable options to treat Non-Hodgkin lymphomas that do not respond to primary therapy.

Dr. Manti Guha

Research Assistant Professor in Cancer Biology, University of Pennsylvania

Associate Research Scientist, Columbia University

My overall research goal is to understand the mechanisms by which mitochondrial defects contribute to pathologies particularly aggressive tumors. I have identified key molecular factors, genetic and epigenetic events by which mitochondrial dysfunction induced signals regulate cellular reprogramming and chromosomal instability. I am currently investigating: (1) the underlying mechanisms by which primary tumor cells accumulate mitochondrial defects; (2) define the mito defects that contribute towards metastasis and to use these molecular markers to stratify tumors at risk for metastasis; (3) develop novel therapeutics targeting the mitochondrial / metabolic vulnerabilities of tumor cells.

Overview of Talk:

Targeting Mitochondrial Heterogeneity To Improve Therapeutic Efficacy In Aggressive Cancers

Aggressive subtypes of breast and esophageal cancers have poor prognosis which emphasizes the need to identify new markers for early diagnosis and treatment. Reports show that altered mitochondrial genome (mtDNA) content in primary tumors correlates with poor patient prognosis. However, it is unknown if mitochondrial defects vary among tumor subtypes and contributes to metastasis and chemoresistance. We analyzed human tumors, 3D organoids, cell lines and the TCGA database to test our hypothesis that mito defects contribute towards tumor aggressiveness. We observed aggressive breast tumor subtypes exhibit higher mitochondrial genomic and functional defects. We therefore utilized heterogeneity in mitochondrial functions among tumors to improve therapeutic efficiency.

Furthermore, in esophageal organoids, mtDNA defects driven oncogenic phenotype is mediated via altered mitochondrial fission. Our findings can be exploited: (1) to develop a mitochondria-based molecular diagnostic approach to stratify patient metastatic risk; (2) mitochondrial/ metabolic aberrations in tumors can be utilized to design precision medicine.

Parallel Symposium: Coping Strategies – Feeding Swallowing, Sleep and Respiratory Symptoms

Blaine Penny (Chair)

Founder and Executive Director of MitoCanada Foundation

Mr. Penny has held several leadership and technical roles throughout his career, including CEO of a start-up engineering firm and Director of the non-profit Geotechnical Engineering (Canada). Mr. Penny will bring his expertise in business management and will represent patient voices on the mitoNET board.

Dr. Peggy Marcon, MD

Staff Gastroenterologist, Hospital for Sick Children, Toronto

Associate Professor, Pediatrics, University of Toronto

Dr. Peggy Marcon is a gastroenterologist in the Division of Paediatric Gastroenterology, Hepatology and Nutrition. She graduated from McNeese State University in Louisiana and then attended medical school at Louisiana State University, Shreveport, graduating in 1983. She undertook her pediatric residency at the Dallas Children's Hospital and University of Texas Southwestern. She then came to the Hospital for Sick Children to complete a fellowship in Gastroenterology. Once on staff she set up the Gastrointestinal Motility Testing Suite. With her interest in gastrointestinal motility she joined and now runs the Dysphagia Clinic where children with medically based swallowing issues are seen. She is part of the clinical and research team in Multidisciplinary Tracheal Esophageal Atresia and Congenital Diaphragmatic Hernia Clinics.

Dr. Kevan Mehta, MD

Assistant Professor, Paediatrics, McMaster University

Paediatric Respirologist, McMaster Children's Hospital

Dr. Kevan Mehta went to medical school in the UK prior to returning to Canada to complete his General Paediatrics Residency at the University of Toronto. He then went on to a fellowship in Paediatric Respiratory Medicine at Sick Kids Hospital, with an additional fellowship in Severe Asthma and Sleep Medicine. Following this, he worked for nearly two years at Sick Kids Hospital in the Sleep Medicine and Long Term Ventilation Programs. He is now an Assistant Professor at McMaster University and Paediatric Respirologist at McMaster Children's Hospital, in addition to working at a community sleep clinic with sleep lab facilities for children as young as four years of age.

Silvana Oppedisano, NP

Paediatric Nurse Practitioner - Enternal Feeding, G-tube Program
Paediatric Medicine

Silvana Oppedisano has worked at SickKids since graduating with a nursing degree from Ryerson University in 1987. She obtained her Master of Nursing from the University of Toronto in 2006 and has held a variety of positions in a number of programs at the hospital including the Burn and Plastic Surgery Program and the Pre-Anesthesia Clinic. Currently, she is the Nurse Practitioner in the G-tube Program in the Department of Paediatric Medicine. She provides consultation for both outpatients in clinic as well as for inpatients of all areas of the hospital, assessing patient's appropriateness, safety and family's readiness for G-tube feeding tube insertion. As an expert in this highly specialized area, she is a resource within the hospital and both in the national and international community.

Lisa Thompson

Patient Advocate

Lisa graduated from Shawnigan Lake School and then attended the University of Washington and the University of Victoria. She completed her degree in neuropsychology. Beyond academics, she was a coxswain on both university rowing crews. She was also part of the Olympic development teams for rowing Canada. Lisa also trained in ballet to a professional level and this remained an integral part of her life until injury forced her to stop.

Lisa became involved with the mitochondrial community in 2012 when a diagnostic oddity brought her doctors to the diagnosis. She reached out to find organizations and although she was able to find them in the US, there were none in Canada. After attending the LHON conference in the US she decided to start a support network for LHON PLUS. She had realized it was an orphan disease that had hardly any

information available for patients and doctors, and her goal was to find patients and then establish research. LHONPLUS.org was born and a support network evolved for patients. Lisa is excited to be able to now be on the board of LHON Canada and work with MitoNet and MitoCanada.

Mitochondrial Innovation Keynote Addresses

Dr. Andrew Nierenberg, MD

Director, Dauten Family Center for Bipolar Treatment Innovation, Massachusetts General Hospital

Professor of Psychiatry, Harvard Medical School

Dr. Nierenberg leads the MGH Dauten Family Center for Bipolar Treatment Innovation, formerly the Bipolar Clinic and Research Program, a center dedicated to finding innovative new treatments, providing high quality clinical care, and educating colleagues, patients, families, and the greater community about Bipolar Disorder. His primary interests are depression, bipolar depression, and novel treatments for mood disorders. Dr. Nierenberg and his colleagues developed an online research infrastructure called the MoodNetwork, a Patient-Powered Research Network (PPRN) that is part of the Patient-Centered Outcomes Research Institute (PCORI). The main aim of the MoodNetwork is to bring together patients, caregivers, and other stakeholders who are affected by mood disorders (i.e., Bipolar Disorder and Unipolar Depression) to form a cohort using patient-reported outcomes and electronical medical records as a national infrastructure for future studies and to participate in comparative-effectiveness studies.

Overview of Talk:

Mood and Mitochondria: PGC-1 Alpha

The PPARs (peroxisome proliferator activated receptors) and their affiliated coactivator PGC-1 alpha are master metabolic switches that not only are beneficial to multiple organ systems, but also promote mitochondrial biogenesis, suppress the destruction of muscle cells through repressing FOXO3, regulate lipid and fat metabolism, decrease inflammation, and are postulated to indirectly promote the gene expression of brain derived neurotrophic factor (BDNF). The key link is that exercise promotes, while inactivity and obesity suppress, the gene expression of PGC-1 alpha. Preliminary evidence supports repurposing these meds and could lead to new therapeutics for mood disorders.

Dr. Sean McKelvey

CEO, Institute for Personalized Therapeutic Nutrition

Sean McKelvey is a pharmacist and CEO for the Institute for Personalized Therapeutic Nutrition. A graduate of the University of British Columbia, Sean is a recognized leader in pharmacy practice change across Canada. Sean has been acknowledged numerous times for his innovative clinical programs including the Canadian Pharmacists Association Patient Care Achievement Award for Innovation and the BC Pharmacy Association Ben Gant award for Innovation. Sean was also awarded the prestigious Len Mark's Award which recognizes an individual for demonstrating outstanding dedication to the advancement of pharmacy. Most recently, he was selected as one of the 2019 Leaders in Pharmacy. Sean is currently the co-investigator on two UBC clinical trials investigating how Therapeutic Nutrition can be used to achieve remission of type 2 diabetes.

Overview of Talk:

Therapeutic Nutrition and Mitochondria

In recent years mitochondria have emerged as central mediators of physiology, regulating not only cellular metabolism but also a range of other cellular functions. Mitochondrial dysfunction is now recognized as a crucial component of pathologies in a number of chronic diseases, including metabolic and degenerative diseases, type 2 diabetes, cancer, heart disease, chronic muscle weakness, movement disorders, and dementia. Targeting mitochondrial dysfunction using Therapeutic Nutrition has recently emerged as a promising strategy to reverse, achieve remission or manage many chronic diseases. In his presentation, Sean will review the clinical implications of Therapeutic Nutrition and its connection to mitochondrial function and bioenergetics.

Hot Topics in Mitochondrial Metabolism

Dr. Carolyn Cummins

Associate Professor, Leslie Dan Faculty of Pharmacy, University of Toronto

Dr. Cummins obtained her undergraduate degree from McGill University in Chemistry with a focus on biological and analytical chemistry. In 2002, she completed her Ph.D. under the guidance of Dr. Leslie Z. Benet at the University of California San Francisco in Pharmaceutical Chemistry. Her studies focused on the interplay between P450s and drug transporters in intestinal drug metabolism. She then took a Howard Hughes Medical Institute postdoctoral fellowship with Dr. David Mangelsdorf at the University of Texas Southwestern Medical Center in Dallas. There, Dr. Cummins used her expertise in P450s and analytical chemistry to

help identify the first ligand for a nuclear receptor in C.elegans. At the same time, she identified a role for the liver X receptor alpha in modulating stress hormone production. Currently, she continues to explore the roles of the liver X receptors and the glucocorticoid receptor in the context of cholesterol homeostasis and diabetes.

Overview of Talk:

My research group is interested in understanding nuclear receptor signaling pathways and designing new therapeutics for the treatment of metabolic disease. We have discovered a series of PPAR partial agonists that have the interesting property of improving metabolic function while also inducing weight loss. I will present an overview of our findings with the compound LDT409 that was studied in the diet-induced obesity model of insulin resistance. I will also present recent data assessing the direct impact of LDT409 on mitochondrial function in brown adipose cells (T37i) by measuring oxygen consumption and extracellular acidification with Seahorse technology.

Dr. Julie St-Pierre

Associate Professor, Department of Biochemistry, Microbiology and Immunology, University of Ottawa

Ottawa Institute of Systems Biology

Canada Research Chair (Tier 1) in Cancer Metabolism

Dr. St. Pierre's research program is focused on metabolic adaptation in cancer progression. The goal of her research program is to identify alternative therapeutic strategies to target metastatic and treatment-resistant breast cancers that are associated with poor patient outcomes. In order to divide, breast cancer cells require energy to build all of the components necessary for making new cells. Dr. St-Pierre's research team has already made seminal discoveries on the importance of altered metabolism in supporting breast cancer growth and progression. They have shown that the PGC-1 family of transcriptional co-activators acts as a central regulator of breast cancer metabolism as well as tumor growth and metastasis. PGC-1alpha regulate numerous metabolic programs to fuel cancer progression, notably glucose and glutamine metabolism. In order to study cancer metabolism, the St-Pierre laboratory uses metabolomics approaches coupled with high-resolution bioenergetics analyses. Her long-term goals are to identify metabolic vulnerabilities of cancer cells in order to develop potential cancer metabolic therapies that could be used either alone or in combination with other anti-cancer drugs.

Overview of Talk:

The central research focus of the St-Pierre laboratory is the understanding of metabolic adaptation to physiological and pathological conditions. We are particularly interested in the plasticity of mitochondrial functions and how they contribute to overall energy homeostasis. During the last decade, our team

contributed significantly to understanding the role of the master regulators PGC-1s in cancer, with a particular focus on poor outcome breast cancers. In this talk, I will highlight our recent discoveries on the role of PGC-1s in supporting metabolic adaptations fueling metastasis and therapeutic resistance.

Dr. Mary-Ellen Harper

Professor, Department of Biochemistry, Microbiology and Immunology, Faculty of Medicine, University of Ottawa

University Research Chair in Mitochondrial Bioenergetics

Director, Mitochondrial Bioenergetics Laboratory

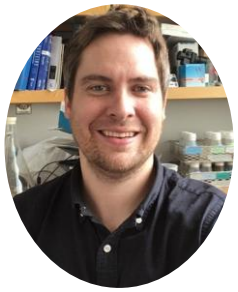
Prof. Harper is a metabolic biochemist; her research focuses on mitochondria and mechanisms and implications of variable metabolic efficiency. She uses integrative approaches spanning from bioenergetic flux, metabolomics, structural analyses, protein post-translational modification, and to dietary studies in mice and humans. She has published over 151 peer-reviewed papers, has supervised 40 undergraduate students, 23 graduate students, and 11 Postdoctoral Fellows. Current research foci include mechanisms of control of the uncoupling proteins; Redox and ROS control of mitochondrial structure and bioenergetics; Implications of mitochondrial dysfunction in obesity, T2DM and cardiac diseases.

Overview of Talk:

A 'Current-Take' on Mitochondrial Proton Leaks

Oxidative phosphorylation (OXPHOS) is responsible for roughly 90% of cellular ATP production. Dysfunctional OXPHOS is associated with many common chronic diseases and some rare genetic diseases. This can have major implications for cellular metabolism, redox, and oxidative damage. Imbalances in redox and reactive oxygen species (ROS) can impair signalling and cause irreversible damage (e.g., to proteins). Proton leaks uncouple respiration/fuel oxidation from ATP synthase, thereby uncoupling OXPHOS and decreasing the efficiency of energy transduction. In a wide range of cell types, proton leaks are responsible for 25-50% of resting cellular oxygen consumption. Leaks may lower ROS production by mitochondria. Mechanisms of proton leak are complex and poorly understood, but involve the uncoupling proteins and the adenine nucleotide translocator. This talk will provide current perspectives on the importance and control of proton leaks.

Hot Topics in Mitochondrial Genetics



Dr. Thomas Hurd

Assistant Professor, Department of Molecular Genetics, University of Toronto

Dr. Hurd's research focuses on studying mitochondrial biology in Drosophila and mammalian systems. In particular, he is interested in determining how mitochondrial DNA is inherited through the female germline, and the role mitochondria play in stem cell function, fate and differentiation in vivo. Dr. Hurd completed his undergraduate degree at the University of Toronto, his PhD at the University of Cambridge in Mike Murphy's laboratory at the MRC Mitochondrial Biology Unit, and his postdoctoral work with Ruth Lehmann at NYU School of Medicine.

Overview of Talk:

Divide and conquer: how deleterious mitochondrial DNA is eliminated in the germline

Unlike nuclear genomes, mitochondrial genomes undergo little recombination, are inherited only maternally, and are subject to a high mutation rate. Consequently, in order to prevent deleterious mutations from accumulating from one generation to the next special selection mechanisms exist in the female germline. Using an allele-specific fluorescent *in situ* hybridization approach, we have visualized germline mtDNA selection *in situ* for the first time. Here we show that mtDNA selection first manifests in the early stages of *Drosophila* oogenesis in differentiating germline cysts. We find that just prior, a reduction in the levels of the pro-fusion protein Mitofusin causes mitochondria to undergo a sustained period of fragmentation. This fragmented phase is necessary to isolate mitochondria preventing them from sharing their contents, which in turn reduces product complementation and allows mitochondria harboring mutant genomes to be selected against. Remarkably, not only is prolonged isolation necessary, but it is also sufficient to induce selection in somatic ovarian tissues where it otherwise does not appreciably occur. Our studies posit a generalizable mechanism to select against deleterious mtDNA mutations that may allow the development of strategies for treatment of mtDNA disorders.

Dr. Neal Sondheimer

Assistant Professor, Department of Pediatrics, University of Toronto

Dr. Sondheimer's research focuses on the regulation of mitochondrial gene expression and the impact of mitochondrial mutations in common and rare disease. Strongly pathogenic mitochondrial mutations exist in a state of heteroplasmy, a mixture of normal and mutated genomes. This state provides opportunities for therapy, as the increase of wild type mitochondrial DNA or the suppression of mutated mitochondrial DNA could improve health. Dr. Sondheimer and his team are investigating mechanisms that could allow shifts in heteroplasmic ratios. He is also interested in the effects of mitochondrial mutations in common disease

and phenotypes such as Alzheimer's disease, aging, and preterm birth. Because bioenergetic capacity is critical to many parts of the body, subtle changes in mitochondrial DNA may have profound effects over time. The mitochondrial genome is the small, densely coding, matrilineally inherited DNA that encodes core subunits of the electron transport chain. Many features of gene regulation are more similar to bacterial and phage systems than they are to gene regulation in the nucleus. Defects in the maintenance of mitochondrial DNA and in the translation of products are known causes of disease. Sondheimer and his team are investigating the dysregulation of mitochondrial transcription as another possible avenue to bioenergetic failure.

Overview of Talk:

Genetic Associations of Mitochondrial Heteroplasmy

Heteroplasmy, the presence of multiple distinct mitochondrial sequences has a critical role in the severity and transmission of mitochondrial disorders due to mtDNA mutation. Despite this, little is known about how the cell might control the emergence or suppression of heteroplasmy. Using genome wide data from nearly 1 million individuals we have characterized heteroplasmy in unaffected individuals and shown that TFAM expression may regulate the heteroplasmic state.

Dr. Yan Burelle

Professor, Department of Cellular and Molecular Medicine, University of Ottawa

Dr. Burelle's research program aims to advance the understanding of the complex mechanisms linking mitochondrial biology to health and disease susceptibility. He has received uninterrupted funding from, the Canadian Institutes and Health Research (CIHR) and the Natural Sciences and Engineering Research Council of Canada (NSERC) for more than a decade. He has published more than 60 articles cited more than 6500 times. His laboratory has developed a broad array of methods to assess multiple facets mitochondrial function (respiration, ROS dynamics, Ca2+ regulation, and cell death signalling) in vitro isolated organelles and permeabilized cells, or in situ in intact cells and organs. These approaches have been used not only in basic studies using animal models, but also in tissues from patients in the context of translational research. His laboratory also studies mitochondrial quality control mechanisms both in vitro with biochemical and confocal imaging approaches, and in vivo with quantitative electron microscopy and mitophagy reporter proteins. Overall, this enables his laboratory to tackle several questions related to mitochondria at multiple levels of biological complexity.

Overview of Talk:

Coping with respiratory chain deficiency through adaptive optimization of the OXPHOS assembly line: Insights from the Leigh Syndrome French Canadian mouse model

LRPPRC is a protein of the PPR family that plays a central role in the stability of mitochondrially encoded mRNA. Mutations of this protein underlies Leigh Syndrome French Canadian (LSFC), a severe disorder characterized by a complex IV assembly defect that predominantly affects liver and brain and leads to unpredictable subacute metabolic crises. To better understand the pathophysiology of this disease, we have developed a mouse model harboring a liver-specific Lrpprc knockout and performed extensive mitochondrial phenotyping. In this talk I will present key phenotypic characteristics of this model and focus on intriguing compensatory changes that appear to take place to preserve residual function.

MITO2019 POSTER PRESENTATIONS

1. 10°C as a superior temperature for prolonged static preservation of donor lungs

Aadil Ali1, Bruno Gomes1, Aizhou Wang1, Rafaela Ribeiro, Marcos Galasso1, Olivia Hough1, Erika Leigh Beroncal2, Thomas Waddell1, Mingyao Liu1, Ana Cristina Andreazza2, Shaf Keshavjee1, Marcelo Cypel1
1.Latner Thoracic Surgery Research Laboratories, Toronto General Research Institute, University Health Network, Canada
2.University of Toronto, Departments of Pharmacology & Toxicology and Psychiatry; The Canada Mitochondrial Network

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Purpose:
Despite remote reports indicating 10◦C to be the optimal temperature for cold static organ preservation (CSP), preservation of lungs in an ice cooler at 4◦C remains the standard strategy in clinical transplantation. Here, we used a device that can keep a donor lung at 10◦C conveniently and compared 10◦C vs. 4◦C during a prolonged period of CSP followed by functional and biological assessment of lung grafts.

Methods:
Lungs were procured from Yorkshire pigs, flushed with a low-potassium dextran solution and randomized into two groups (n=5 each): CSP at 4◦C vs. CSP at 10◦C. After 36h of CSP, lungs were subjected to 12h of normothermic ex vivo lung perfusion (EVLP) with hourly functional assessment.

Results:
During 12h of EVLP, lungs stored at 10◦C presented superior physiological parameters compared to 4◦C indicated by significantly lower airway pressures, higher lung compliances, and better oxygenation ($p = <0.0001$ each). Metabolic profiles of the EVLP perfusate (glucose, lactate, pH) were significantly more favorable in the 10◦C group compared to 4◦C ($p = <0.0001$ each). Furthermore, the 10◦C group had significantly less inflammation demonstrated by lower levels of pro-inflammatory cytokines IL-1β, IL-6, and IL-8 in the EVLP perfusate ($p = <0.0001$ each).

Conclusion:
With simple controllable refrigerators, 10°C preservation is easily achievable and provides significantly superior CSP in comparison to conventional 4°C storage. This could potentially remarkably extend the clinical and transportation logistics in lung transplantation. Biological assessment of mitochondrial functional markers is underway to gain insight on the therapeutic mechanism behind this temperature difference.

Conflict of Interests/Disclosures:
M.C, T.W., S.K. and M.L. are founders of XOR Labs Toronto and M.C, T.W. and S.K are founders of Perfusix Canada and consultants for Lung Bioengineering.

2. Molecular pathophysiology and stem cell treatment for mitochondrial diseases: insights from the French Canadian variant of Leigh Syndrome.
A. Cuillerier 1, V. Cadete 2, G. Cairns 1, J. Rossi 1, D. Stewart 2, **Y. Burelle** 1;
1 University of Ottawa, Ottawa, ON, CANADA, 2 Ottawa Hospital Research Institute, Ottawa, ON, CANADA.

Leigh Syndrome is the most common pediatric presentation of a genetic mitochondrial disease, with a highly heterogenous clinical phenotype and over 75 causative mutations. There are currently no effective treatments available for patients. Recent findings show that mesenchymal stem cells (MSCs) promote repair of injured tissues through various mechanisms including direct mitochondria transfer to target cells with impaired mitochondria, significantly improving their outcome by replacing dysfunctional organelles, a property that is relevant in the context of genetic mitochondrial diseases. This project aims to test the therapeutic potential of MSCs for genetic mitochondrial disorders using the French-Canadian variant of Leigh Syndrome (LSFC) as a disease model. In order to identify the effects of MSCs on the disease model's mitochondrial phenotype, both the paracrine and the direct effects of MSCs are observed. The paracrine effect is studied through coculture of LSFC fibroblasts and MSCs with the transwell system, and by exosome treatment of LSFC fibroblasts. After treatments, mitochondria respiration, as an indicator of mitochondrial function, is assessed using Seahorse technology. In addition to the paracrine effect, direct mitochondria transfer is monitored using co-culture of stably transfected MSCs and LSFC patients' fibroblasts (GFP-MFF, mCherry-Mito7) and fluorescent microscopy. To assess the functional impact of the co-culture, mitochondrial respiration is measured with the Seahorse. Overall, we expect a positive impact of MSCs on the mitochondrial phenotype of LSFC cells. This could suggest that MSCs may be part of a potential viable treatment for genetic mitochondrial diseases including, but not limited to, Leigh Syndrome.

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3. Characterization of mitochondrial health and neuronal activity in cerebral organoids: a way forward in precision medicine
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Mitochondrial health is essential for proper neuronal signaling. Thus, it is believed that mitochondrial dysfunction underlies the deficits in neuronal activity, leading to the clinical manifestation and development of neuropsychiatric disorders. A key challenge in the field is that this evidence remains correlational. This problem stems from the lack of appropriate patient-derived models that can simultaneously evaluate mitochondrial health and neuronal signaling. Current methods rely on postmortem brain samples, animal models or two-dimensional neurons from induced pluripotent stem cells (iPSCs) derived from fibroblasts. These tools lack complexity and neural circuits, limiting our ability to develop targeted mitochondrial therapies. To address this problem, we used three-dimensional cerebral organoids (COs) to interrogate mitochondrial health and neuronal activity within the same patient. Here, we developed COs from iPSCs derived from patient peripheral blood mononuclear cells (PBMCs) and compared them to COs derived from conventional human embryonic stem cells (hESCs). We demonstrated that COs generated from either source exhibit: (1) preserved mitochondrial genetics, function and treatment response across all stages of differentiation from PBMCs to iPSCs to COs or hESCs to COs; and (2) measurable neuronal activity. In the clinics, the use of PBMCs is vast and readily accessible compared to fibroblasts obtained from invasive biopsies. As a result, we expect our approach to be a starting point for more sophisticated patient-derived brain models from PBMCs for the study of the impact of mitochondrial dysfunction on neuronal activity in a larger cohort of patients with neuropsychiatric disorders – a way forward in precision medicine.

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4. TFEB AND TFE3 exert distinct roles in mitochondrial adaptations in skeletal muscle cells

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Damaged mitochondria are removed to limit toxic effects through a selective form autophagy, termed mitophagy, in which dysfunctional organelles are poly-ubiquitinated, engulfed in an autophagosomal membrane and transported to the lysosome for degradation. Acute exercise induces mitophagy to promote the optimization of the mitochondrial pool, while also promoting lysosomal biogenesis by activating the transcriptional regulators TFEB and TFE3. The purpose of this study was to evaluate the role of the transcriptional regulators of lysosomal biogenesis following exercise. Thus, we hypothesize that the lysosomal alterations support mitophagy and are crucial for mediating chronic contractile activity (CCA)-induced mitochondrial changes. TFEB and TFE3 expression was reduced in murine (C2C12) skeletal muscle cells using siRNA and then subjected to electrical stimulation (5Hz, 10V, 3hr/day, 3 days) to induce CCA. The absence of TFEB decreased PGC-1α, the master regulator of mitochondrial biogenesis, basally and abolished the CCA-induced elevation in PGC-1α, which was not seen in the absence of TFE3. COX IV, a nuclear-encoded mitochondrial marker, increased with CCA by ~2.4-fold even in the absence of TFEB and TFE3. In contrast to this, the mtDNA-encoded COX I increased with the absence of TFEB in both control and CCA by ~2 fold, while the absence of TFE3 reduced COX I by 21%. Preliminary data also suggest that mitophagy flux, measured by the fluorometric ratio of mtKeima, is reduced in the absence of TFE3 following an acute bout of CA. These data suggest that TFEB and TFE3 may regulate mitochondria in response to CCA albeit by distinct mechanisms.

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5. The expression of mitochondrial and lysosomal proteins in the absence of LAMP2 in mouse skeletal muscle

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The maintenance of a healthy pool of mitochondria is dependent on the balance of mitochondrial biogenesis and degradation, known as mitophagy. The final stage of mitophagy requires the fusion of the autophagosome, which engulfs dysfunctional mitochondria, with lysosomes containing hydrolytic enzymes. Fusion of the two organelles creates an autolysosome and requires the lysosomal protein LAMP2. The purpose of this project was to evaluate the effect LAMP2 in muscle on mitochondrial turnover by utilizing the gastrocnemius of whole body LAMP2 KO mice. LAMP2 KO mice exhibited an increase in the adapter protein p62, responsible for tethering the autophagosome to the dysfunctional cargo. Similarly, the LC3-II to LC3-I ratio was increased in mice lacking LAMP2. These results indicate an accumulation of autophagosomes that are not properly degraded. TFEB, the master regulator of lysosomal and autophagy genes, was increased in KO mice compared to WT, potentially in an attempt compensate for the absence of LAMP2. We next investigated mitochondrial proteins in these mice. PGC-1α, the master regulator of mitochondrial biogenesis, and UQCRC2, an electron transport chain protein, were elevated in the KO mice compared to WT. However, COXIV protein content was not affected. Interestingly, COX activity, another measurement of mitochondrial content, was significantly increased in the KO mice. This could likewise suggest an aberration in the autophagy process. Lamp2 is required for the clearance of cellular organelles. In its absence, an increased transcriptional drive for both lysosomal and mitochondrial biogenesis was evident, suggesting the existence of retrograde signaling pathways to the nucleus.

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6. Interrogating the Role of PINK1/Parkin-Mediated Mitophagy in Remote Ischemic Preconditioning-Induced Hepatoprotection in Murine Hemorrhagic Shock-Resuscitation

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Introduction/Background: Hemorrhagic shock-resuscitation (HSR) represents a form of global ischemia reperfusion injury (IRI). IRI following HSR has a myriad of mitochondrial dysfunctions. Autophagosome mediated clearance of uncoupled mitochondria— 'mitophagy'—is important in re-establishing cellular/organ integrity. Remote ischemic preconditioning (RIPC) has been shown to augment autophagy in hepatic IRI and facilitate multi-organ protection in both animal models and human patients. The PINK1/Parkin-mediated pathway is one of the main stress-induced forms of mitophagy.

Methods: Here, we utilize an *in vivo* murine model of HSR-IRI to interrogate the role, if any, of PINK1/Parkin mediated mitophagy in the hepatoprotective effects conferred by RIPC. After microvascular cannulation (with or without RIPC via four cycles of hindlimb occlusion) of the carotid and femoral arteries, C57BL/6 wild-type and Parkin KO mice are subjected to 2h of controlled hemorrhage to a mean arterial pressure of 30mmHg followed by fluid resuscitation and 2h of monitoring before sacrifice. Blood and organs are collected, followed by a series of molecular analyses, including: subcellular fractionation, ALT and CRP1 plasma levels, inflammasome ELISAs, necrosis area quantification, immunofluorescence microscopy, Western blot densitometry, and transmission electron microscopy.

Results: Offspring and breeding parents were all confirmed to be true Parkin KOs. HSR+RIPC WT (n=9) animals displayed significantly decreased ALT levels as compared to HSR WT animals (n=10) ($p<0.02$). For Parkin KO mice initial evidence shows RIPC to no longer be protective (n=5). All sham animals had no liver injury. ELISAs, Western blots, electron microscopy, necrosis area quantification and immunofluorescence microscopy are all currently in-progress.

Conclusions/Discussion: If Parkin is shown to be vital in RIPC-induced hepatoprotection, other organ systems can be studied. Thus, PINK1/Parkin-mediated mitophagy may become an innovative therapeutic target.

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7. The mitochondrial-enhancing drug Olesoxime improves mitochondrial function in quadriceps and diaphragm and improves muscle volume in a mouse model of Duchenne muscular dystrophy

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Mitochondrial dysfunction is thought to be a secondary contributor to muscle weakness in Duchenne muscular dystrophy (DMD) – a severe muscle-wasting disease affecting ~1:3500 males. Previously we demonstrated mitochondrial dysfunction occurs in diaphragm and quadriceps of mice with DMD. Olesoxime (TRO19622) is a mitochondrial-targeting compound that prevents mitochondrial dysfunction, improves motor function and increases life span in other neurodegenerative diseases. We hypothesized that olesoxime administration will improve mitochondrial bioenergetics in these muscles compared to vehicle controls. Male D2.B10-DMDmdx/2J (D2.*mdx)* mice received a daily oral gavage of corn oil supplemented with olesoxime (DRUG) (30mg/kg body weight) or without (VEH, vehicle) from age 10 days to 28 days. Age-matched controls (WT) were compared to both disease groups. As assessed by computed tomography, whole body lean muscle volume was significantly decreased in DMD compared to WT but was significantly increased in the DRUG group compared to VEH. Total trunk fat was not different between these groups but were significantly decreased compared to WT. These improvements in muscle volume were related to a significant decrease in serum creatine kinase with olesoxime as determined by spectrofluorometry (VEH vs DRUG). High resolution respiratory showed significantly improved mitochondrial respiration in quadriceps and diaphragm with olesoxime but were still significantly lower than WT. Olesoxime improved whole body lean volume, serum creatine kinase and mitochondrial respiration in quadriceps and diaphragm. Ongoing research will examine whether olesoxime improves histological markers of the disease (fibrosis, atrophy) and force as well as lowers H2O2 emission and mitochondrial induction of apoptotic cell death pathways.

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8. Grape Seed Extract Improves Mitochondrial Function Disrupted by Hyperglycaemia in Endothelial EA.hy926 Cells

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Diabetes mellitus is a metabolic disease characterized by chronic hyperglycaemia, which causes redox unbalance and mitochondrial dysfunction. This study evaluated the capacity of grape seed extract (GSE) to modulate oxidative stress, nitric oxide levels, mitochondrial dysfunction and apoptosis in endothelial EA.hy926 cells in high glucose condition. Besides the possible toxic effects of GSE was evaluated in a zebrafish embryos model. Results showed that GSE was able to enhance cell viability and avoid the disturbance in redox metabolism induced by high glucose. Besides, GSE was able to avoid mitochondria dysfunction and the increase in p53 and poly-(ADP-ribose) polymerase expression induced by high glucose. These effects were attributed to the increase on expression of sirtuin 3, a protein able to regulate mitochondrial function. GSE in an effective concentration did not show toxic effects in zebrafish embryos model. Taken together, these data contribute for understanding of the mitochondrial disorder induced by hyperglycaemia as well as establishing the conditions required to minimize these alterations, which will lead to the future pharmacological interventions for diabetic patients.

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9. Investigating the role of the weight loss compound LDT409 in brown adipocytes

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Brown adipose tissue (BAT) is a unique thermogenic tissue for altering energy expenditure and fuel metabolism by producing heat through uncoupling protein UCP1. Stimulation of peroxisome proliferator-activated receptors (PPARs), a sub-class of nuclear hormone receptors expressed in BAT, upregulates expression of UCP1; therefore, pharmacologically targeting BAT through UCP1 may be a promising approach to treat obesity and diabetes. Our lab has developed a novel a pan-active PPAR compound LDT409, which is a fatty acid-like compound derived from cashew nut shell liquid. Our lab has also shown that chronic treatment with LDT409 reversed diet-induced metabolic abnormalities and upregulated the expression of *Ucp1* in diet-induced obese (DIO) mice. Herein, we investigated the systemic effect of LDT409 on energy expenditure both *in vivo* and *in vitro*. Metabolic parameters including respiratory exchange ratio (RER) and energy expenditure, were assessed in DIO mice using indirect calorimetry. Oxygen consumption rate (OCR) in T37i brown adipocyte cells was measured using a Seahorse XFe96 analyzer. DIO mice treated with LDT409 exhibited reduced fat mass and decreased RER, which indicates an increased fat utilization. Intriguingly, there was no significant effect of LDT409 on energy expenditure in DIO mice; whereas, LDT409 treatment robustly increased energy expenditure in T37i cells compared to vehicle treatment (measured by OCR). Additionally, treatment with LDT409 for 16 hrs significantly induced lipolysis and upregulated the expression of thermogenic and fatty acid oxidation genes in T37i cells. Taken together, LDT409 induces BAT thermogenesis *in vitro* and fatty acid utilization *in vivo* which may provide a therapeutic treatment for obesity.

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10. Central Nervous System Drugs and its Interaction with Mitochondrial Function

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The purpose of this analysis is to review medications with adverse reactions and gene interactions in relation to mitochondrial interaction. Mitochondrial cybrid mutations and nuclear interactions will also be screened in the mitochondrial gene interactions. The analysis focuses on three categories of drugs that act on the central nervous system (CNS): anti-epileptics, anesthetics, and psychotropics. The CNS consists of the brain and the spinal cord, which receives information and coordinates activities of the whole human body. Therefore, drugs that act on the CNS may bring profound effects to the human body; thus, we should be cautious when using them. We hope to present lists of medications along with their potential toxic interaction with the mitochondria that can help patients make informed decisions when discussing treatment options with healthcare professionals.

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11. Antioxidant and Anti-Inflammatory effect of a Selenium, L-Carnitine and Guarana supplement to improve the quality of life of multiple sclerosis patients

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Introduction: Oxidative stress (OE) plays a major role in the pathogenesis of multiple sclerosis (MS) triggering, demyelination, axonal damage, inflammation and fatigue. It is possible that a multisuplement consisting of Selenium (S), L-carnitine (C) and guaraná (G, *Paulinia cuppana*) (SCG) could attenuated these symptoms1,2. **Objectives:** the study evaluated antioxidant, anti-inflammatory SCG-effects. **Methods:** two protocols were performed: (1) SH-SY5Y cells and peripheral blood cells to determine safety and antioxidant effect and (2) BV-2 cells and peripheral blood cells to determine inflammatory parameters3. SCG-effect on cells was determined by spectrophotometric tests and flow cytometry.

Anti-inflammatory effect was evaluated by flow cytometry cell cycle analysis. OE-markers (lipoperoxidation, protein carbonylation, nitric oxide, reactive oxygen species (ROS) and DNA damage index) were performed in both models. **Results:** the obtained results showed a decreased in oxidative and apoptotic markers of SH-SY5Y cells and peripheral blood cells. Also, it was observed a decrease in inflammatory levels. **Conclusion:** results suggest that SCG-supplement could be safe and effective in controlling OE-MS, inflammation and fatigue.

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12. Mitochondrial DNA Content and Oxidation in Bipolar Disorder and its Role Across Brain Regions

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Bipolar disorder (BD) is a chronic neuroprogressive disorder that causes significant impairment to patients' quality of life. The specific underlying pathology of bipolar disorder remains unknown. In this study, we aim to investigate the role of mitochondrial dysfunction in BD by evaluating mitochondrial electron transport chain complex I subunit NDUFS7 protein expression; mtDNA content; common deletion; and oxidation in the Broadmann area 24 (BA24), cerebellum, hippocampus, and prefrontal cortex from patients with BD, schizophrenia, and non-psychiatric controls. We aim to evaluate region specific effect between BA24 and cerebellum, since it is obtained from the same patient. Kim *et al.* (2016) reported decreased protein expression of NDUFS7 in the prefrontal cortex of patients with BD. Here we demonstrated no changes in NDUFS7 in other brain regions, increased levels of mtDNA content in hippocampus of patients with BD and decreased mtDNA oxidation in BA24 and cerebellum of patients with BD and schizophrenia, respectively. Paired analysis between BA24 and cerebellum revealed increased NDUFS7 levels and mtDNA content in cerebellum of patients with BD or schizophrenia but not in controls. Also, we found a positive correlation between NDUFS7 and mtDNA content of mitochondrial complex I subunits (ND4 and ND5) when combining brain regions. Lastly, we demonstrate no alteration in the levels of mtDNA deletion between different diagnoses. Our study further supports the involvement of mitochondrial dysfunction in BD and schizophrenia. Furthermore, our results support the importance of the prefrontal cortex and cerebellum within the pathology of BD and schizophrenia.

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13. Essential in vivo role of skeletal muscle UVRAG in mitochondrial dynamics and EGFR Signaling

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Autophagy is a physiological 'self-eating' process that can either promote cell survival or activate cell death in eukaryotic cells. In skeletal muscle, autophagy is important in the maintenance of muscle mass and function that is critical to sustain mobility and regulate metabolism, particularly with aging. Ultraviolet radiation resistance-associated gene (UVRAG) regulates early stages of autophagy and autophagosome maturation, while also playing a key role in endosomal fusion and trafficking. The purpose of this project is to understand the specific roles of UVRAG in skeletal muscle biology. Skeletal muscle specific UVRAG knockout mice were generated using the Cre-LoxP system under the control of Myf6 promoter that is exclusively expressed in skeletal muscle. Myf6 Cre+ UVRAGfl/fl (KO) mice were compared to littermate Myf6 Cre+ UVRAG+/+ (WT) controls under basal conditions on normal chow diet. With aging, KO mice developed accelerated sarcopenia and displayed impaired muscle function compared to WT littermates. These mice also displayed mitochondrial dysfunction, altered muscle mitochondrial morphology with increased mitochondrial fission, increased muscle Fgf21, and EGFR accumulation reflecting defects in endosomal trafficking. To determine whether increased EGFR signaling had a causal role in muscle dysfunction, mice were treated with an EGFR inhibitor, Gefitinib, which partially restored markers of muscle and mitochondrial dysfunction. Constitutively active EGFR transgenic expression in UVRAG deficient muscle demonstrated additive and non-overlapping effects of UVRAG and EGFR in muscle function, with EGFR affecting muscle fiber type but not mitochondrial homeostasis. Our results show that UVRAG is crucial in maintenance of muscle mass and function with aging with distinct mechanisms in the differentiation pathway.

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14. Altered mitochondrial fusion in metabolically flexible cells drives defensive glutathione synthesis

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Mitochondria are highly dynamic organelles. Alterations in mitochondrial dynamics are causal or are linked to numerous neurodegenerative, neuromuscular, and metabolic diseases. It is generally thought that cells with altered mitochondrial structure are prone to mitochondrial dysfunction, increased reactive oxygen species generation and widespread oxidative damage. The objective of the current study was to investigate the relationship between mitochondrial dynamics and the master cellular antioxidant, glutathione (GSH). We reveal here that MEFs lacking the mitochondrial fusion machinery, display limited oxidative damage due to elevated levels of GSH. While exploring the mechanism of this GSH upregulation, we discovered widespread metabolic remodeling that have poised cells lacking the inner membrane fusion GTPase OPA1 towards GSH synthesis. Metabolomics and 13C isotopic labeling experiments revealed altered citric acid cycle intermediates, increased GSH precursors and increased GSH synthesis in cells lacking OPA1. The level of GSH in OPA1 KO cells reached saturation as treatment with the GSH precursor and antioxidant n-acetylcysteine was unable to increase GSH levels. Finally, metabolic flexibility was a requirement for GSH upregulation following OPA1 deletion and as such postmitotic neurons completely lacked this response. Thus, our results demonstrate a novel role for mitochondrial fusion in the regulation of GSH synthesis; our results suggest that cysteine availability is not limiting for GSH synthesis in conditions of mitochondrial fragmentation; and our results provide a possible explanation for the heightened sensitivity of certain cell types to alterations in mitochondrial dynamics.

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15. Cannabinoids downregulate nuclear-coded subunits in respiratory complexes of adolescent brain mitochondria

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Dependable assessment of potential harm associated with Cannabis consumption is important in populations at risk. This is the case of adolescents for whom exposure to Cannabis may lead to addiction, anxiety, depression and neurocognitive deficits akin to those found in schizophrenia, autism, intellectual disability, and mood disorders. A common denominator underlying symptoms in these disorders are cellular changes in the frontal cortex that result in abnormal connectivity and dysfunctional network activity. We were therefore interested in assessing the impact of Cannabis exposure on cellular phenotypes of the frontal cortex. Cannabis is pharmacologically complex, containing at least 100 different cannabinoids with putative biological activity. These plant constituents mainly produce their effects by interacting with different components of the endocannabinoid system, which comprises: Cannabinoid GPCRs (CB1R, CB2R and GPR55); L type Ca2+ channels; transient receptor potential channels; nuclear receptor transcription factors; and orphan GPCRs. Furthermore, the cell-specific distribution of most of Cannabis targets and associated effectors is for the most part poorly characterized adding an additional level of complexity that is only starting to be considered. The existence of these compounding variables implies a myriad of possible ligand-target interactions contributing to *in-vivo* responses of cannabinoids. Such diversity makes it practically impossible to choose relevant targets, cells or processes on which to focus our attention to detect harm potential. For this reason, we turned to single cell phenotyping, a novel powerful technique which allowed us to evaluate cortical actions of cannabinoids on a non-hypothesis driven basis. Hence, for the study adolescent mice were repeatedly exposed to the phytocannabinoid ☐9-THC (THC), or the synthetic ligand WIN 55,212-2 (WIN). Following treatment their frontal cortices were dissected and single-cell

transcriptomes obtained. The latter revealed that repeated THC or WIN administration induced significant downregulation of genes coding for mitochondrial respiratory complexes. Changes were ligand and cell-specific. In particular, both treatments downregulated multiple subunits in all five respiratory complexes of pyramidal neurons of layer 2/3, but THC was the only treatment producing such reduction in microglia. Transcriptomic changes were verified by immunohistochemistry. Taken together these results show that cannabinoids have the potential to negatively affect mitochondrial function in neuronal and non neuronal brain cell types.

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16. Two-in-one: UV radiation simultaneously induces mitochondrial ROS-dependent NETosis and Apoptosis

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NETosis is a unique form of neutrophil death that differs from apoptosis. However, whether NETosis and apoptosis can occur simultaneously in the same neutrophil is unknown. We show that increasing doses of ultraviolet (UV) irradiation increases NETosis, which is confirmed by myeloperoxidase colocalisation to neutrophil extracellular DNA. Increasing UV irradiation increases caspase 3 activation, mitochondrial reactive oxygen species (ROS) generation and p38, but not ERK, phosphorylation. Inhibition of mitochondrial ROS production, but not NADPH oxidase (NOX) activity, suppresses UV-induced NETosis, indicating that UV induces NOX-independent NETosis that is dependent on the mitochondria. Like classical NOX-dependent and -independent NETosis, UV-induced NETosis requires transcriptional firing for chromatin decondensation. Collectively, these studies indicate that increasing doses of UV irradiation induce both apoptosis and NETosis simultaneously, but the ultimate outcome is the induction of a novel form of mitochondrial ROS-dependent NETosis, or "ApoNETosis". This novel form of neutrophil death may be relevant to UV-mediated diseases such as skin cancer and Lupus.

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17. Morphine interacts with IDH and alters mitochondrial metabolism in glioma brain tumors

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Background:
Isocitrate dehydrogenase (IDH) is a key metabolic enzyme found in the mitochondria and cytoplasm. It is responsible for the conversion of isocitrate to **αα**-ketoglutarate, a central metabolite of the TCA. Cytoplasmic IDH (IDH1) produces NADPH and is therefore involved in mitigating intrinsic oxidative

stress. In over 80% of low-grade gliomas, IDH1 is mutated, resulting in the disruption of multiple mitochondrial metabolic pathways, the consumption of NADPH, and increase in oxidative stress. Interestingly, patients with the mutation have better prognoses than those without. We have found that morphine, a commonly used analgesic amongst cancer patients, is an inhibitor of IDH1. Our research explores the interaction between morphine, IDH1, and drug-induced mitochondrial dysfunction in mimicking the IDH1 mutation phenotype.

Methods and Results:

We inoculated tumors in mice using the U87 IDH1 wild-type glioma cell line and treated with clinically relevant morphine concentrations for 30 days. Tumors were analysed for metabolic changes through LC/MS metabolomics. Energy transfer molecules including ATP, ADP, and GTP were amongst the 30 metabolites effected by morphine. Significant changes to mitochondrial metabolites in the citric acid cycle, glycolysis, and pentose phosphate pathway were observed. *In vitro* investigation of changes to oxidative stress by flow cytometry indicated that morphine treated cells had 4 times the level of reactive oxygen species (ROS) compared to control. In the presence of naloxone, a μ-opioid receptor antagonist used to account for opioid mediated effects, ROS levels were 2-fold higher following morphine treatment.

Conclusion:

Drugs can heavily contribute to altering the energy state and metabolomic health of cells by impacting mitochondrial function. Morphine treatment significantly altered mitochondrial metabolic pathways, as well as increasing ROS, independent of μ-opioid receptor activation. This phenotype mirrors that of gliomas with the IDH1 mutation, thus suggesting the possibility for improved patient prognosis. Our work illustrates the effect of interactions between pharmacology and mitochondrial function through metabolism.

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18. From Biohacker to Citizen-Scientist: A Case Study

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Introduction and Background: A two-year observational case study report of a 55-year-old female with a rare genetic condition (MERRF) for which there is no current therapy or cure. The patient also presented with multiple symmetric lipomatosis (MSL) which caused a dramatic decrease in her perception of quality of life. A resection surgery was performed which triggered a metabolic crisis for the patient and resulted in a further deterioration of her health condition and her placement on long term disability.

Methods: The patient independently researched, applied, and documented a multifaceted program of lifestyle interventions that was outside the standard of care. She relied on her medical team, academics, scientific papers, family members and social media as resources. She tracked all interventions with commercially available apps and provided regular updates to her medical team throughout.

Results: The patient was successful in both achieving and sustaining an improvement in her overall health as verified by objective and subjective measurements of the targets at the two-year mark. She has returned to work and plans to continue with the lifestyle intervention indefinitely. Critically, the professional relationship between the patient and medical team was challenged but also strengthened by this experience through a shared decision-making process which will allow ongoing research collaboration.

Discussion: The quality of the therapeutic relationship between a patient and a medical team is inseparable from health outcomes. In this case, what kept both the patient and the medical team at the table despite the challenges?

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19. Prevalence of mitochondrial disease and psychiatric conditions across Ontario

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Background
Dysfunction of the mitochondria, a key organelle responsible for cellular energy production, can have profound effects on neurotransmission. Continuous dysfunction may contribute to alterations in neuronal functioning implicating cognition, memory and other forms of neuronal plasticity. For example, impaired neurotransmission is evident in patients with bipolar disorder. However, there is currently no direct evidence for an association between mitochondrial dysfunction and psychiatric conditions.
Methods
Using multi-linked health administrative data from Ontario's single-payer health insurance program (OHIP), we identified Ontario residents hospitalized for mitochondrial disorders (ICD-9 code 277.87; ICD-10 codes G71.3, E88.8) between April 1988 and March 2018. We summarized characteristics of the mitochondrial disease population at the time of first identifiable hospitalization. We assessed prevalence of mood disorders and other mental health conditions defined as two or more outpatient billings within a 2-year period, or 1 or more hospitalizations for reasons related to mental health disorders or addiction.
Results
We identified 2668 unique individuals hospitalized for mitochondrial disorders in the study period. Within this group, 66% received care as defined for a mood disorder (52%) or other mental health condition (42%) between July 1991 and March 2018. In comparison, 40% of the general Ontario population received care in the same period.
Implications
These findings represent the first population-based cohort study of mitochondrial disease in Canada. The data will support future analyses and better understanding of the mitochondrial disease population. In particular, the burden of mental health disorders and addiction in patients with mitochondrial disease warrants deeper investigation.

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20. Açaí's (Euterpe oleracea Mart.) anti-neuroinflammatory effect on BV-2 microglia cells with rotenone-induced mitochondrial complex I dysfunction

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Neuropsychiatric illness, such as bipolar disorder (BD), still have unclear pathophysiology. To understand it better, Andreazza et al (2010) have described the association between BD and oxidative stress via mitochondrial complex I dysfunction. Kim et al (2015) showed that this dysfunction could be related to neuroinflammation. On the other hand, Machado et al (2016) showed that *Euterpe oleracea* Mart. (açaí) is capable to recover mitochondrial complex I function in neuron-like cells. Currently, our research group described that açaí can act as an anti-inflammatory agent in macrophages. The objective of this study was to evaluate the anti-neuroinflammatory potential of açaí extract through mitochondrial complex I recovering. BV-2 microglia cells were exposed to a concentration-response curve of açaí extract during 24, 48 and 72h to evaluate the *per se* effect. Microglias were activated with the most effective concentration of rotenone and treated with açaí extract, followed by determinations of cellular proliferation, levels of reactive oxygen species (ROS), nitric oxide (NO), extracellular dsDNA, pro-inflammatory cytokines and cell cycle modulation. Most of tested açaí extract concentrations were unable to modulate cellular proliferation by itself. 200 nM of rotenone was capable to induce microglia mitochondrial dysfunction and increase proliferation. When exposed to rotenone and treated with açaí extract, microglia cells presented recovered cellular proliferation index, reduced levels of ROS, NO, extracellular dsDNA and proinflammatory cytokines. Cell cycle also showed to be similar to untreated cells. These results suggest that açaí extract has anti-neuroinflammatory effect via mitochondrial complex I modulation.

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21. Identification of Novel Mitochondrial DNA Maintenance Factors Using a Mitochondria targeting Chemical Probe in CRISPR-Cas9 Genomic Screens

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Mitochondria are known as the "powerhouse" of eukaryotic cells. In addition to providing ATP molecules and necessary metabolic intermediates for cell growth, these organelles are also responsible for calcium homeostasis, apoptosis and other essential processes determining cellular fate. Damage in mitochondrial DNA (mtDNA) results in dysfunction of mitochondria and has been linked to many health problems, such as cancer progression and neurological diseases. However, pathways and factors involved in mtDNA repair are poorly characterized, majorly due to the high impermeability of mitochondria. Our group has developed a mitochondria-penetrating peptide (MPP) that can carry small

molecules specifically to the mitochondrial matrix. The goal of this project is to apply MPP conjugated to a DNA-binding oxidizing agent (mt-Ox) in genomic CRISPR-Cas9 screens to identify novel factors responsible for mtDNA maintenance and oxidative damage repair. After validation of the compound and condition optimization of the treatment, the genomic knockout screen has been successfully performed. Top gene hits, which knockout made the cells more sensitive to mtDNA oxidative damage, potentially play important roles in mtDNA maintenance and repair pathways. The selected gene hits are currently under validation for their synergistic effect with mt-Ox. Functional studies will also be performed to confirm the roles of these genes in mtDNA maintenance as well as general health of mitochondria (e.g. membrane potential, oxygen consumption).

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22. Organization of mitochondrial DNA: an intrinsic process regulated by mitochondrial dynamics

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Mitochondria are important for maintaining cellular homeostasis and mutations in mitochondrial DNA (mtDNA) causes many mitochondrial diseases. mtDNA is organized in discrete foci within mitochondria called nucleoids. Although the process of mtDNA replication is well defined, the processes regulating segregation and organization of nucleoids across the mitochondrial network are still unclear. This is especially important in a number of mutations in nuclear genes that affect mtDNA content, including genes regulating mitochondrial dynamics, the process by which mitochondria fuse and fragment. To define the mechanisms by which mitochondrial dynamics affect nucleoid distribution, we developed a new tool to measure nucleoid distribution along mitochondrial tubules, as well as their relationship to the network features (ends, junctions). We found that in human fibroblasts, nucleoids avoid each other at short distances but are correlated at greater distances. This suggests that there is a complex process regulating the organization of nucleoids, which limits the distribution of any two nucleoids closer to each other. To study the role of mitochondrial dynamics in this process, we analysed nucleoid distribution in human fibroblasts from patients with defective mitochondrial fission (non-muscle myosin II protein (MYH14) and dynamin related protein (DRP1) mutants). We found that these cells have reduced numbers of nucleoids and altered nucleoid distribution. Our results suggest that mitochondrial fission is required specifically to separate nucleoids following mtDNA replication, but not for their subsequent distribution within mitochondrial networks.

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23. Peripheral Biomarkers of Mitochondrial Dysfunction in Serum of Youth Bipolar Disorder Patients

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Mitochondrial dysfunction has been implicated in the pathophysiology of bipolar disorder (BD). Impediment of mitochondrial oxidative phosphorylation results in a shift toward anaerobic respiration and lactate production. Elevated CNS lactate levels in adults with BD inform the need to evaluate lactate in peripheral samples and early in the course of BD. Furthermore, there exists a recent surge of investigations looking at circulating cell-free mitochondrial DNA (ccfmtDNA) as a potential biomarker as they are released from cells under physiological stress, apoptosis, or bioenergetic compromise. One-hundred and five adolescents (n=64 for BD and n=41 for HC) were included. Serum lactate level was measured using a commercially available colorimetric kit. Serum ccf-mtDNA concentration was measured using quantitative polymerase chain reaction from ccfDNA purified by commercially available spin columns. Diagnoses and mood symptoms were evaluated using semi-structured interviews. There is an increase in serum lactate level of adolescents with BD vs HC, but not ccf-mtDNA. Among BD adolescents, depression symptoms were negatively correlated with ccf-mtDNA levels. Lactate was positively correlated with ccf-mtDNA in the overall sample; when examined by diagnosis, this association remained in BD, but not HC. These preliminary results indicate that elevated lactate is observed even among adolescents early in their course of BD, that the association between lactate and ccf-mtDNA appears to be specific to BD, and that ccf-mtDNA is associated with depression symptoms in adolescent BD. In addition, the effect of psychotropic medications used in the treatment of BD on peripheral lactate and ccf-mtDNA requires further investigation.

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24. Glucocorticoid-Induced Adipose Tissue Remodeling is Attenuated by LXRβ Antagonism

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Excessive glucocorticoid (GC) exposure, either from endogenous or exogenous sources, potentiates the development of diabetes and obesity. Undesirable metabolic side-effects greatly limit the long-term use of GCs as immunosuppressants. Induction of brown adipose tissue (BAT) and re-balancing white adipose tissue (WAT) are new pharmacologic strategies to combat obesity. GCs are known disruptors of BAT/WAT function. Our group demonstrated that LXRβ is required for GC-induced side effects in the liver but not the beneficial anti-inflammatory effect of GCs. The discovery of this new GC/LXRβ crosstalk led to the hypotheses that LXRβ antagonism may be therapeutically beneficial to prevent GCinduced dysfunction in BAT and WAT. To test this, LXRα-/- mice were treated for 5d with vehicle, 5mg/kg dexamethasone (Dex, synthetic GC agonist), and/or 40mg/kg GSK2033 (GSK, non-selective LXR antagonist). As expected, Dex increased BAT mass and fat accumulation, and GSK was able to abrogate these effects. Dex-treated mice were unable to guard their body temperature with cold exposure, but GSK co-treatment protected against this drop. Dex increased WAT and adipocyte size, and this was reversed by GSK co-treatment. At the transcriptional level, GSK attenuated the Dexmediated downregulation of thermogenesis in BAT as well as the upregulation of lipogenesis in WAT. Similar changes were observed in WT mice. Overall, our data suggest that LXRβ antagonism can reverse the disturbance in BAT and WAT function caused by GC-treatment in an *in vivo* model, highlighting the potential role of LXRβ antagonists in combating the negative effects of excessive GC exposure on the development of obesity.

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25. Regulation of Mitochondrial quality by P53 in denervated skeletal muscle

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Persistent muscle disuse, as with aging or immobilization, promotes progressive weakness and atrophy of skeletal muscle along with reductions in mitochondrial content, and has considerable consequences on strength, mobility, and overall health. p53 is known to respond to disturbances in the cellular environment to restore homeostasis. Previous studies from our lab and others have elucidated a role for p53 in regulating skeletal muscle mitochondrial content and function, as well as contributing to muscle atrophy following prolonged disuse. We investigated whether p53 is necessary for mediating mitochondrial quality control (MQC) and muscle atrophy following muscle disuse by subjecting p53 muscle-specific knockout (mKO) and wild-type (WT) mice to unilateral denervation-induced disuse for 7 days. Hindlimb muscles were collected to assess the extent of muscle atrophy, changes in mitochondrial content and function, and the protein expression of markers of MQC. Reductions in hindlimb mass of denervated muscle corresponded to reductions in mitochondrial content, however divergent responses in mitochondrial function and regulation were observed. Respiration was similarly impaired between genotypes, whereas ROS was further enhanced in mKO mice. Nuclear PGC-1α and mature Tfam were elevated while mitochondrial PGC-1α was reduced in denervated muscle of either animal. Denervation induced increases in markers of MQC including upregulation of autophagy/mitophagy, lysosomal and UPR proteins, however in many cases this response was blunted in mKO muscle. This suggests a dysregulation of MQC in the absence of p53 within skeletal muscle subjected to denervation and indicates a potential role of p53 in contributing to organelle maintenance during muscle atrophy.

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26. Mitochondria and redox homeostasis as targets of Araucaria angustifolia extract in neuropsychiatric diseases

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Neuropsychiatric diseases (ND), are often associated with impairments in mitochondrial function, and oxidative damage that can lead to neuronal injury. However, pharmacotherapy still cannot efficiently control oxidative stress and neuronal redox imbalance. Natural products could represent an alternative to help subjects suffering from these diseases to minimize neuronal impairments as well as recover their quality of life. Araucaria angustifolia , one of the main pine species in South America, presents important therapeutic history in folk medicine. A. angustifolia extract (AAE), obtained from the natural waste

named bracts, is rich in flavonoids, molecules able to regulate cellular redox metabolism. Considering that mitochondrial complex I dysfunction is consistently reported in ND, we aimed to investigate whether AAE is able to avoid mitochondrial dysfunction induced by rotenone, a well-studied inhibitor of complex I, in neuronal-like SH-SY5Y cells. Cell viability was assessed by ELISA assay; production of reactive oxygen species (ROS) was determined using a fluorometric assay; protein levels of mitochondrial complex I, relevant to ROS generation, were evaluated by multiplex ELISA followed by immunoblotting. Results demonstrated that AAE post-treatment increased complex I protein expression and activity levels against mitochondrial dysfunction caused by rotenone. Analyzing the subunits of complex I, increased NDUFS7 and NDUFS8 protein levels, were found. These data were accompanied by a reduction in the generation of ROS, thus controlling the neuronal oxidative damage. Natural AAE exerts in vitro neuroprotective effects, thus making them a potential candidate for drug design and a possible strategy to ND therapy._

Keywords: mitochondria; psychiatric disorders; oxidative stress
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27. Exocytosis of mitochondrial proteins requires mitochondria-derived vesicles

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Recently, Cell-Cell communication has emerged as an important tool in understanding disease mechanisms, and a therapeutic target. Specifically, cells secrete a range of extracellular vesicles (EV), that act as communication devices by transferring proteins, DNA and RNA between cells. Several studies have reported that mitochondrial proteins accumulate in these vesicles, but their role or mechanism through which this occurs remain poorly understood. Here we show that mitochondria derived vesicles (MDVs) play an important role in the selective release of mitochondrial proteins in EVs. MDVs are small vesicles that carry specific mitochondrial cargo destined to be degraded in peroxisomes and lysosomes. MDVs are also involved in immune regulation thought MHC I antigen presentation, which requires the protein Snx9. We demonstrate that Snx9 is also involved the inclusion of some mitochondrial proteins in EVs. Specifically, knockdown of Snx9 inhibited the formation of MDVs positive for the mitochondrial matrix protein mtHSP70, and their release as EVs. In contrast, MDVs and EVs positive for the outer mitochondrial membrane TOM20 were not affected, demonstrating the selective, MDV-dependent incorporation of mitochondrial cargo in EVs. Importantly, deletion of OPA1, an inner membrane protein required for mitochondrial fusion and maintenance of cristae structure, selectively caused loss of MDVs and prevented the exocytosis of inner membrane proteins. Our findings indicate that MDVs selectively target mitochondrial proteins towards EV formation in a process that is dependent on the presence of Snx9 and OPA1. These results could thus provide important insight into the mechanisms regulating cell to cell communication by EVs.

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28. Targeting mitochondrial metabolism pathways to direct polarization of monocytes/macrophages to therapeutic inflammation-suppressing subtypes

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BACKGROUND & AIM: Monocytes/macrophages (MΦs, as a heterogeneously differentiated population) are capable of adopting a diverse spectrum of functionalities from proinflammatory to inflammation-resolving. Chronic diseases often involve metabolic dysregulation that impacts the pro-inflammatory to inflammation-resolving MΦ ratio. Typically, this dysregulation translates as increased mitochondrial glycolysis, which toggles MΦ phenotype/functionality into persistent pro-inflammatory subtypes. Using small molecules that target mitochondrial glycolysis and/or oxidative phosphorylation pathways, we aim to exogenously toggle MΦs into inflammation-resolving subtypes for local administration in chronic inflammatory disease settings such as osteoarthritis.

METHODS: For a targeted screening of small molecules, healthy donor peripheral blood CD14+ MΦs or a monocytic cell line THP-1 are cultured for ≤48h in the presence of known or predicted glycolytic inhibitors or TCA cycle activators. Polarized MΦs are assessed by gene/protein expression of cytokines (IL10/IL1β/TNFα/IL6/IL1RA/IL12A), surface markers (CD163/CD206/HLA-DR/ CD86), and function (reactive oxygen species production, dextran endocytosis, Treg induction). Outcomes are compared against naïve and traditional cytokinepolarized inflammation-resolving MΦ controls.

RESULTS & CONCLUSIONS: 9 small molecules at 3 dose levels were screened for 48h gene expression. We have identified 2 molecule-dose combinations that upregulate expression of anti-inflammatory IL10 and IL1RA, respectively, by ≥ 5-fold and pro-inflammatory profiles resembling the cytokine-polarized controls. Additional functional characterization is ongoing. Developing novel approaches to modulate mitochondrial function supports the development of MΦ-targeting therapies. Promoting oxidative function is a novel approach to clinical applications of polarization that may prove to be equal or superior to costly cytokine-based strategies.

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29. The role of mitophagy on muscle stem cell fate, health and repair capacity

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Skeletal muscles have a remarkable capacity to repair and regenerate in response to injury by virtue of their unique population of resident muscle stem cells (MuSC). Recently, several studies have reported that mitochondria are important regulators of fate and function in various types of stem cells including

MuSCs. Furthermore, accumulation of dysfunctional mitochondria is reported to lead to MuSC aging, premature commitment and impaired self-renewal. This led us to hypothesize that maintenance of an optimally functioning population of organelles through degradation of damaged mitochondria by mitophagy is important for self-renewal and muscle repair. To test this, a cardiotoxin (CTX) injury model of the *Tibialis Anterior* muscle was used in mice harboring a knockout of PINK1, a key regulator of mitophagy. Preliminary results indicate that at 14 days post injury, the number of cells positive for the differentiation marker MyoD is increased in *PINK-/-* compared to WT. Cross sectional area of newly regenerated fibers is also increased compared to WT. However, the number of cells positive for the MuSC marker PAX7 is reduced in absence of PINK1. These data suggest that loss of PINK1 mediated mitophagy promotes commitment of MuSCs at the expense of self-renewal. While this may enhance muscle repair following acute injury, the impairment of self-renewal could ultimately lead to depletion of the MuSC pool and impaired muscle regeneration under more chronic conditions or with aging. This question is being pursued using acute and chronic injury models as well as studies in primary myoblasts and single muscle fiber cultures.

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30. Quadruplex Mediated Reduction of a Pathogenic Mitochondrial Heteroplasmy

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Disease-associated variants in mitochondrial DNA (mtDNA) are frequently heteroplasmic, a state of co-existence with the wild type genome. Because heteroplasmy correlates with the severity and penetrance of disease, improvement in the ratio between these genomes in favor of the wild type, known as heteroplasmy shifting, is potentially therapeutic. We evaluated known pathogenic mtDNA variants and identified those with the potential for allele-specific differences in the formation of non-Watson-Crick G-quadruplex (GQ) structures. We found that the Leigh Syndrome (LS)-associated m.10191C variant promotes GQ formation within local sequence in vitro. Interaction of this sequence with a small molecule GQ-binding agent, berberine hydrochloride, further increased GQ stability. The GQ formed at m.10191C differentially impeded the processivity of the mitochondrial DNA polymerase gamma (Pol γ) in vitro, providing a potential means to favor replication of the wild type allele. We tested the potential for shifting heteroplasmy through the cyclical application of two different mitochondria targeted GQ binding compounds in primary fibroblasts from patients with m.10191T>C heteroplasmy. Treatment induced alternating mtDNA depletion and repopulation and was effective in shifting heteroplasmy towards the non-pathogenic allele. Similar treatment of pathogenic heteroplasmies that do not affect GQ formation did not induce heteroplasmy shift. Following treatment, heteroplasmic m.10191T>C cells had persistent improvements and heteroplasmy and a corresponding increase in maximal mitochondrial oxygen consumption. This study demonstrates the potential for using small-molecule GQ-binding agents to induce genetic and functional improvements in m.10191T>C heteroplasmy.

31. GSkeletal Muscle autophagy and mitophagy are altered in the time course of hindlimb denervation
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Mitophagy is a quality control mechanism that clears dysfunctional mitochondria via them lysosomes. Since chronic muscle disuse promotes fibre atrophy concomitantly with reductions in mitochondrial content and function, this work aims to better understand the processes of mitophagy in the context of muscle disuse.We employed a hindlimb denervation protocol in which we unilaterally sectioned the peroneal nerve in rats for 1,3 or 7 days. The tibialis anterior and extensor digitorum longus muscle were excised for muscle protein measures and isolation of subsarcolemmal (SS) and intermyofibrillar (IMF) mitochondria for functional assessment (i.e. respiration and ROS production) and protein analysis. To investigate the changes in autophagy and mitophagy flux, a subset of animals was treated with colchicine (4mg/kg/day) for 2 days prior to sacrifice to inhibit autophagic breakdown. To further assess mitophagy flux, mice overexpressing mt-keima, a mitochondrial-targeted probe that fluoresces green when exposed to the pH of the cytosol, and red when exposed to the pH of the lysosomes, underwent unilateral sciatic nerve denervation for 1,3 or 7 days. Here, we show that mitochondrial content is reduced with denervation, whereas function is impaired. Elevations in autophagy/mitophagy occurred at 1- and 3-days post-denervation, prior to the upregulation of autophagy and lysosomal markers at 7 days post-denervation, suggesting that the intrinsic activity of the autophagosomal breakdown pathway is sufficient in the early time course. However, with prolonged denervation, we observed an up-regulation of mitophagy/autophagy proteins, which was not met by increases in flux rates, potentially leading to the accumulation of dysfunctional mitochondria.

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32. Mitochondrial ROS regulates NADPH oxidase-independent NETosis: A novel function to neutrophil mitochondria
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Neutrophils are short-lived terminally-differentiated innate immune cells (55-70% of blood Leukocytes) that infiltrate the site of infection and injury. These cells degranulate, phagocytose or cast neutrophil extracellular traps (NETs; NETosis, a form of suicidal cell death with NET formation). NETs trap invading pathogens, but too much of NETs contributes to many pathological conditions including sepsis, autoimmune diseases (lupus), atherosclerosis, cystic fibrosis and cancer metastasis. However, the mechanistic details of NETosis have not been fully elucidated. We aimed to determine novel regulatory steps of NETosis by both hypothesis driven experiments and drug screening approaches. In terms of metabolic processes, neutrophils are interesting cells. Neutrophils are highly active cells and rapidly generate enormous amounts of ATP, however, they use glycolysis but not oxidative phosphorylation. Hence, the function of mitochondria in differentiated neutrophils was unknown. Our studies identified

that neutrophils use mitochondria to generate reactive oxygen species (ROS) that is necessary for NADPH oxidase-independent NETosis. Hence, we assigned a novel immune function to neutrophil mitochondria. Furthermore, we have identified many factors and processes necessary for the mitochondrial ROS-mediated NETosis including pH (range from 6.6 to 7.8), calcium and transcriptional firing. Drug screening studies further identified some NETosis regulatory drugs that affect mitochondrial ROS and NADPHindependent NETosis. Mitochondria may also directly involve in releasing their own DNA in vital NET formation, in which neutrophils survive after NET formation. Hence, newly identified mitochondria-mediated NETosis regulatory mechanisms and NETosis regulatory drugs will be helpful to treat some of the NET-related diseases.

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33. A targeted Agps knockdown in H9c2 cells drives a mitochondrial remodelling consequently to disrupted plasmalogen synthesis.

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Plasmalogens constitute a subclass of glycerophospholipids essential for cell homeostasis. The synthesis of plasmalogens is initiated in the peroxisome by three key enzymes, GNPAT, FAR1 and AGPS. Disorders affecting the synthesis of plasmalogens cause disabilities, some of which being reported to affect the heart. However, consequences originating from a deficiency in plasmalogens in cardiac cells need to be further examined. Methods: The knockdown of Agps by CRISPR-Cas9 in H9c2 was validated by qPCR and immunoblot. Moreover, the level of plasmalogens was measured using mass spectrometry-based analysis. Finally, the cell line phenotype was characterized using qPCR and immunoblot targeting markers of i) mitochondrial function (biogenesis, dynamics and fatty acid utilization), ii) stress of the endoplasmic reticulum (ER) and iii) apoptosis. Results: AGPS reduction was validated in i) gene expression (-58%) and ii) protein expression (-78%), decreasing the plasmalogen pool (-76%).
This decrease is accompanied by clues of mitochondrial remodeling: i) biogenesis: reduction of Pgc1-α and β (-27%; -61%), ii) dynamics: reduction of Opa1 and Mff (-15%), iii) FA metabolism: reduction of the carriers Cd36 (-52%) and Cpt1 (-51%), followed by a reduction of β-oxidation genes: Vlcad and Lcad (-22%; -13%). This overall reduction in gene expression seemingly leads to increased cellular stress of the ER (+31% Chop) and a reduction of non-cleaved CASPASE-3 expression (-32%). Conclusion: Altogether, also validated in another independent cell line, these results support a mitochondrial remodeling in H9c2 cells caused by a plasmalogen deficiency, which will be closely examined on a functional and signaling level.

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34. Role of mitochondrial energetics in stem cell maintenance

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Metabolic reprogramming is a multifunctional process that provides the bioenergetic fuel necessary for cell survival and proliferation. In particular, cancer cells modify their metabolism to sustain proliferation

and adapt to the changing tumour microenvironment (i.e. reduced nutrient and oxygen). Among the cells within a tumour, cancer stem cells (CSCs) represent metabolically distinct subpopulations with stem-like properties and are main causes of relapse, metastasis and drug resistance of a cancer. The exact mechanisms regulating CSC formation and maintenance remains unresolved, but recent evidence suggest that mitochondrial dynamics, the process of mitochondrial fusion and fission, could play an important role. To address the role of mitochondria in CSC maintenance, we used breast cancer cell model to generate differentiating and stem like cells. Both phenotypes appear to share a common metabolic profile that is characterized by increased utilization of ATP derived from glycolysis. Stem like cells exhibit fragmented mitochondria, decrease oligomerization of the mitochondrial fusion protein OPA1, and increased mtROS, consistent with their glycolytic phenotype. However, they maintained a mitochondrial membrane potential similar to that of differentiating cells and were highly sensitive to electron transport chain inhibitors. Our results thus suggest that even though CSC have a fragmented mitochondrial network, they still require mitochondrial function for their survival.

Key words: Mitochondria, Breast cancer, Stem cells, Metabolism, Dynamics

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35. Mitochondrial Genetic Variation in Nicotine Dependency

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Cigarette smoking is a chronic addiction caused primarily by nicotine and remains a serious public health concern.Nicotine dependency (ND) has a heritability rate of ~50%, suggesting that genetic factors play a role on the underlying mechanisms of ND. Nicotine appear to perturb mitochondrial functioning. Here, we aimed to examine whether variants within mitochondrial DNA (mtDNA) and nuclear-encoded mitochondrial genes are associated with measures of ND. **Methods**: A sample of 488 nicotine dependent individuals had their DNA genotyped using Infinium Global Screening Array (Illumina). Data was cleaned using standard quality control protocol. Age at onset was the measure of ND. We performed gene and gene-set analyses to test the association between 72 nuclear-encoded mitochondrial genes (involved in oxidative phosphorylation) using MAGMA pathway tool. Linear regression was used to test mtDNA common variants, and One-Way ANOVA to test mitochondrial haplogroups (mitochondrial sequences sharing specific sets of geographically related variants). **Results**: Results for MAGMA gene and gene-set analyses, as well as mtDNA haplogroup analysis were not statistically significant. Three single nucleotide polymorphisms in mtDNA were significantly associated with the age of onset of smoking which included: A750A ($P_{corrected}$ = 1.18E-11) in the *MT-RNR1*, A1438A ($P_{corrected}$ = 5.37E-07) in the *MT-RNR2*, and A4769A ($P_{corrected}$ = 6.80E-09) in the *MT-ND2*. **Conclusion:** The findings suggest common variants within

mtDNA may contribute to the genetic vulnerability to smoking addiction. Replication of the findings in larger ND sample is underway.

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36. Development of an ELISA-based protocol for accessible, high-throughput characterization of mitochondrial function

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The five protein complexes of the electron transport chain (ETC) in the human mitochondria are crucial to mitochondrial redox function and are believed in to be implicated in disease. However, current methods of determining mitochondrial activity lack accessibility and reproducibility. The goal of this project is to develop an ELISA-based procedure that detects the expression of specific functional subunits in the five complexes of the ETC, as it was hypothesized that the expression of these functional subunits is directly related to the activity of the ETC complexes that contain these subunits. To begin, a literature review was performed to identify functionally relevant subunits in all five complexes of the human mitochondria, and succinate dehydrogenase B (SDHB) in Complex II was chosen for preliminary studies., To date, an ELISA was standardized for optimal detection of SDHB expression in THP-1 cells. Moving forward, Complex II activity would be determined using commercial assays and correlated to SDHB expression in THP-1 cells, and eventually in other cell types. This investigation into the correlation between activity and expression would then be extended to the other mitochondrial ETC complexes. Establishing the correlation between activity and expression of ETC subunits allows for the development of a cost-effective, high-throughput, ELISA-based method of predicting mitochondrial activity for diagnostic or research purposes in the treatment of mitochondrial diseases.

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37. Mitochondrial Expression and Peripheral Inflammation in Adolescent Bipolar Disorder and Depression

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Several psychiatric illnesses exhibit both mitochondrial dysfunction and elevated inflammation, yet treating each complication separately has not been clinically effective. The NLRP3 inflammasome is a multiprotein complex which integrates mitochondrial stress and activates inflammatory responses. Previously we found NDUFS7, a subunit of mitochondrial complex I, to be downregulated in bipolar postmortem brain samples. This study investigates mitochondrial dysfunction as a biological source of NLRP3 upregulation in peripheral blood samples from adolescents with bipolar disorder (BD) and major depressive disorder (MDD).

Gene expression of NLRP3 inflammasome components and 16 nuclear encoded mitochondrial complex subunits were measured by quantitative reverse transcription polymerase chain reaction on RNA in whole blood collected from adolescents with mood disorders. The cohort consisted of control (n=18), bipolar (n=10) and depression (n=14) groups, with an age range of 13-19 years. Circulating cell free mitochondrial DNA copy number was measured in matching plasma, and mitochondrial volume was quantified in peripheral blood mononuclear cells using confocal microscopy.

A reduction in mitochondrial volume per cell was observed specifically in adolescent BD. Both BD and MDD patients had lower levels of NDUFS7 gene expression, while only MDD patients had increased NLRP3 gene expression. Adolescence is a critically important period, not only for mood disorders to emerge, but also for early stage intervention. These results support our previous NDUSF7 findings; suggest a distinction in early disease pathophysiology; and hold promise for the development of novel biological targets that can effectively track illness progression in adolescent mood disorders.

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38. Neurostructural Correlates of Glutathione Peroxidase 3 rs3792797 Polymorphism in Adolescents with and without Bipolar Disorder

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Background: Oxidative stress has been implicated in the etiopathology of bipolar disorder (BD). Relatedly, BD is among the most heritable, and therefore genetic, psychiatric disorders. However, no prior study has examined oxidative stress genes in relation to neuroimaging phenotypes in BD. We evaluated two oxidative stress genes, glutathione peroxidase 3 (GPX3) rs3792797 and super oxide dismutase 2 (SOD2) rs4880, in relation to structural neuroimaging phenotypes among adolescents with BD early in their course of illness.
Methods: T1-weighted images were obtained from 69 Caucasian adolescents (BD=37; healthy controls (HC)=32; GPX3 AC/AA= 26; GPX3 CC=43; SOD2 AC/AA=53; SOD2 GG=15). Images were processed using FreeSurfer to obtain surface area, volume and thickness values for cortical regions of interest (ROIs; dorsolateral prefrontal cortex (dlPFC), ventromedial PFC (vmPFC), ventrolateral PFC (vlPFC), caudal anterior cingulate (cACC)), along with hippocampal volume.
Results: There were significant diagnosis-by-GPX3 interaction effects on cACC thickness ($F=4.50$; $p=0.038$) and vmPFC volume ($F=4.34$, $p=0.04$). The cACC interaction was due to greater thickness in BD GPX3 A carriers vs. HC A carriers ($F=5.32$, $p=0.02$) and BD CC homozygous group ($F=4.25$, $p=0.04$). Findings did not remain significant after correction for multiple comparisons. There were no significant findings for SOD2.
Conclusion: This exploratory study yields preliminary evidence that GPX3 rs3792797 differentially impacts brain structure in regions that are relevant to BD. Further studies evaluating additional neuroimaging phenotypes, blood levels of oxidative stress markers, and neurocognition are warranted to extend upon these findings.