BIOGRAPHICAL SKETCH

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NAME: Picard, Martin

eRA COMMONS USER NAME: PICARDM

POSITION TITLE: Herbert Irving Associate Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE	Completion Date MM/YYYY	FIELD OF STUDY
McGill University, Montreal, Qc	BS	05/2007	Physiology/Neuroimmunology
McGill University, Montreal, Qc	PhD	10/2012	Mitochondrial biology of aging
Center for Mitochondrial and Epigenomic Medicine, University of Pennsylvania, PA	Postdoctoral	05/2015	Mitochondrial genetics

A. Personal Statement

My group's work has contributed to shift our view of mitochondria from that of a powerhouse to a signaling organelle, functioning as an interface between human behavior and molecular processes inside the cell. As a postdoctoral fellow in Doug Wallace's laboratory, I initially mapped the dose-response effects of mitochondrial DNA (mtDNA) mutations on nuclear gene expression, showing that mitochondria extensively regulate the human (epi)genome. With my lab, working to understand how mitochondria communicate not only with the nucleus but also with each other, we identified novel structures in human tissues – mitochondrial nanotunnels and inter-mitochondrial junctions – that enable their mito-mito communication intracellularly. Expanding the scope of these studies on mitochondrial communication from organelle to organism, we used mouse genetics and discovered that mitochondrial signaling regulate in a quite systematic manner the neuroendocrine, metabolic, and brain gene expression responses to psychological stress. To understand the long-term effect of stressors on cell energetics, my group has established a laboratory platform to measure the mitochondrial health index (MHI), which has provided the first evidence in humans that psychological states influence mitochondrial function. We have now optimized our MHI platform for small brain samples and documented in the mouse brain large-scale regional variation that map onto functional specialization across cortical and sub-cortical regions (in preparation). My lab has also described how acute psychological stress in humans rapidly elevates serum circulating cell-free mtDNA (ccf-mtDNA), and that mtDNA release is triggered *in vitro* by stress mediators, revealing the mitochondrial genome as a potential stress-inducible hormone. To study mitochondrial communication in aging, we have also developed a cellular lifespan model that recapitulated epigenetic aging signatures from human tissues.

In the clinic, we have conducted single-cell studies in patients with inherited mitochondrial disorders and used imaging and computational methods to define the nature of the human mitochondrial network and discover how pathogenic mtDNA mutations expand over time. Combined, our work at the intersection of clinical medicine, psychological stress, and computational mitochondrial biology has given rise to the field of mitochondrial psychobiology. I have now assembled a team (Drs. Bennett, De Jager, Wager, Thiebaut de Schotten, Assuras) that brings together one of the largest AD cohort, mitochondrial biology, and neuroimaging to understand the influence of mitochondrial function on human brain circuitry and its relevance to Alzheimer's disease.

1. **Picard M**, McEwen BS. Mitochondria impact brain function and cognition. *Proc Natl Acad Sci U S A*. 2014;111(1):7-8. PMID: 24367081
2. **Picard M***, Trumpff C, Burelle Y. Mitochondrial psychobiology: Foundation and applications. *Curr Opin Behav Sci* 2019; 28:142-151. PMID: In progress
3. **Picard M**, et al. Mitochondrial functions modulate neuroendocrine, metabolic, inflammatory and transcriptional responses to psychological stress. *PNAS* 2015;112(48):E6614-23. PMID: 26627253
4. **Picard M***, Prather AA, Puterman E, Cuillerier A, […], Epel E. A mitochondrial health index sensitive to mood and caregiver stress. *Biol Psychiatr* 2018; 84(1):9-17. PMID: 29525040

B. Positions and Honors

Positions and Employment

01-03/2013	Visiting scholar, Novo Nordisk Foundation Center for Basic Metabolic Research-Epigenetics Laboratory, Copenhagen University, Copenhagen
2015 - 2018	Assistant Professor, Columbia University Irving Medical Center, York NY
2015 -	Visiting scholar, Wellcome Centre for Mitochondrial Research, Institute of Neuroscience, Newcastle University School of Medicine, Newcastle UK
2018 -	Affiliate member, Zuckerman Mind Brain Behavior Institute, Columbia University
2019 -	Herbert Irving Associate Professor, Columbia University Irving Medical Center, Departments of Psychiatry and Neurology, Division of Behavioral Medicine, New York NY

Other Experience and Professional Memberships

2004 - 2012	Member, Respiratory and Epidemiology Clinical Research Unit, McGill University, Canada
2009 - 2012	Member, Neuromuscular Research Group, Montreal Neurological Institute, McGill University
2009 - 2012	Fellow, Psychosocial Oncology Training Program, CIHR and McGill University
2010 - 2012	Fellow, Systems Biology Training Program, CIHR and McGill University
2010 -	Peer reviewer: Aging Cell; Am J Physiol Cell Physiol; Am J Physiol Endocrinol Metab; Am J Physiol Reg Integr Compar Physiol; Anesthesiology; Appl Physiol Nutr Metab; Bioessays; Biochem J; Biol Psychiatr; Biology; BBA Biomembranes; BBA Mol Basis Dis; Brain Behav Immun; Chromosome Res; Circ Res; Clin Sci; EBiomed; Exper Gerontol; J Appl Physiol; J Bioeng Biomed Sci; J Clin Med Res; J Physiol; Microsc Microanal; Mitochondrion; Mol Psychiatr; Nat Commun; Neurosci Biobehav Rev; Plos One; Psychosom Med; Psychoneuroendocrinol; PNAS; Sci Rep; Stress
2011 -	Member, American Physiological Society
2011 -	Member, American Psychosomatic Society
2013 -	External reviewer: Danish Council for Medical Sciences; National Science Center of Poland
2014 -	Conference review committee, American Psychosomatic Society
2014 -	Member, International Society of Psychoneuroendocrinology
2016 -	Co-Chair, Columbia University Seminars (USEM) on the Future of Aging Research
2017 -	Fellow, Columbia University Aging Center Research

Honors (selected)

2006	Alvin Shrier Physiology Scholarship, McGill University, Department of Physiology
2007	Undergraduate Summer Research Award, National Science and Engineering Research Council (NSERC) of Canada
2008	Alexander Graham Bell Canada Graduate Scholarship (Masters), NSERC of Canada
2008	Masters Training Scholarship, Fonds de Recherche en Santé du Québec
2008	Graduate Fellowship (declined), McGill University Health Center Research Institute
2009	Alexander Graham Bell Canada Graduate Scholarship (Doctoral), NSERC of Canada
2009	McGill Provost's Graduate Fellowship, McGill University
2009	Master's Research Excellence Award, McGill University
2011	EGSS Doctoral Award for Research and Professional Excellence, McGill University
2011	Age+ Prize, Canadian Institute of Health Research
2011	David L. Montgomery Award for Leadership and Excellence, McGill University
2011	Prix Acfas Desjardins 2011 (Doctoral, All disciplines), Association Francophone Pour le Savoir
2012	Journal of Cell Science Traveling Fellowship, Journal of Cell Science (London)
2012	Michael Smith Foreign Study Supplement, NSERC of Canada
2013	Caroline Tum Suden Professional Opportunity Award, American Physiological Society
2013	Young Investigator Colloquium Award, American Psychosomatic Society
2017	Herbert Irving Named Professorship, Columbia Irving Institute
2017	Frontiers in PNI lecturer, Psychoneuroimmunology Research Society (PNIRS)
2019	Neal E Miller New Investigator Award, Academy of Behavioral Medicine Research (ABMR)
2019	Rising Stars Lecture, NIH

C. Contribution to Science

1. MITOCHONDRIAL ALLOSTATIC LOAD. Integrating our clinical and pre-clinical findings in the context of the allostatic load "wear-and-tear" model of chronic stress, I formulated with my mentor Bruce McEwen the concept of Mitochondrial Allostatic Load (MAL). MAL refers to the structural, functional and molecular changes that occur within mitochondria in response to prolonged stress, leading to transcriptional dysregulation, cellular dysfunction, and systemic disease. I first began testing this model by working with unique mouse strains which harbor targeted molecular defects in energy production and mitochondrial redox-regulating enzymes. As predicted by the MAL model, abnormal mitochondrial function regulates transcriptional and systemic stress responses, including the major neuroendocrine systems such as the hypothalamic-pituitary-adrenal (HPA) and sympathetic adrenal- medullary (SAM) axes, metabolic, and inflammatory changes linked to human disease. My lab has also developed the mitochondrial health index (MHI) platform, which has sufficient sensitivity and throughout to profile mitochondrial health in frozen blood cells. We have used this approach to produce the first evidence that positive mood influence mitochondria within days. This line of work places my group in a unique position to make a substantial contribution to the field of stress pathophysiology by rigorously addressing the contribution of mitochondrial energetics in stress regulation and the brain-body axis.
   a. **Picard M***, Juster RP, McEwen BS. Mitochondrial allostatic load puts the 'gluc' back in glucocorticoids. *Nat Rev Endocrinol*. 2014;10(5):303-10. PMID: 24663223
   b. **Picard M**, McManus MJ, Gray J, Nasca C, Moffat C, Kopinsky P, Seifert E, McEwen BS, Wallace DC. Mitochondrial functions modulate neuroendocrine, metabolic, inflammatory and transcriptional responses to psychological stress. *PNAS* 2015;112(48):E6614-23. PMID: 26627253
   c. **Picard M***, Prather AA, Puterman E, Cuillerier A, […], Epel E. A mitochondrial health index sensitive to mood and caregiver stress. *Biol Psychiatr* 2018; 84(1):9-17 PMID: 29525040
   d. **Picard M***, McEwen BS. Psychological stress and mitochondria: A Systematic review (Part I) PMID: 29389736 / A Conceptual Framework (Part II) PMID: 29389735. *Psychosom Med* 2018;80(2):126-153

2. MITOCHONDRIAL PSYCHOBIOLOGY AND CCF-mtDNA. Integrating the above ideas with mitochondrial omics we have coined the term *mitochondrial psychobiology*, which defines the available mitochondrial laboratory toolbox to understand how behavioral/psychosocial experiences and biological processes intersect with molecular processes within mitochondria. The framework highlights biological specificity (e.g., mitochondrial differences across cell types) and biological complexity established in the mitochondrial field, and computational approaches (e.g., machine learning) focused on predictive modeling to achieve robust generalizable conclusions. This model also emphasizes that stress adaptation is essentially driven by energetic processes through the brain and body, and highlights how adaptive stress systems are under energetic constraints. Further to our work on MAL, we recently discovered that induced psychological stress triggers the specific release of serum mtDNA (circulating cell-free mtDNA, ccf-mtDNA). We have also introduced new methods to the field of psychoneuroendocrinology by using machine learning to identify individualized predictive biomarker patterns of ccf-mtDNA stress reactivity. Our ongoing studies in this domain are mapping in humans the stability of mitochondrial behavior over time in specific cell types, contributing to lay the foundation for this emerging field.
   a. Trumpff C, Marsland AL, Basualto C, Martin JL, Carroll JE, Sturm G, Gu Z, Vincent A, Kaufman BA, **Picard M***. Acute psychological stress increases serum circulating cell-free mitochondrial DNA. *Psychoneuroendocrinol* 2019; 106:268-276. PMID: 31029929
   b. Trumpff C, Marsland AL, Sloan RP, Kaufman BK, **Picard M***. Predictors of ccf-mtDNA reactivity to acute psychological stress identified using machine learning classifiers: A proof-of-concept. *Psychoneuroendocrinol* 2019 107:82-92. PMID: 31112904
   c. **Picard M***, Trumpff C, Burelle Y. Mitochondrial psychobiology: Foundation and applications. *Curr Opin Behav Sci* 2019; 28:142-151. PMID: In progress

3. MITOCHONDRIAL COMMUNICATION and REGULATION OF GENE EXPRESSION. At the intracellular level mitochondria communicate with each other and with the cell nucleus. By combining multiple experimental approaches including high-resolution electron microscopy with tomography (3D imaging), synthetic linker technology to manipulate mitochondrial interactions in living cells, mouse genetics to probe molecular composition, and exercise/inactivity physiology to establish physiological significance, I led an effort to discover inter-mitochondrial junctions (IMJs). This work produced the first physical evidence of information exchange between mitochondria. In relation to mito-nuclear signaling, I initially used high-throughput sequencing and bioinformatics to map the dose-response effects of mtDNA mutations on the

transcriptome. This defined core principles of mitochondrial retrograde signaling via epigenetic regulation of gene expression. My lab has since developed a primary cell culture approach to longitudinally map conserved lifelong nuclear DNA methylation alterations that occur in response to aging and mitochondrial signaling. These discoveries are significant because they show that mitochondria physically and functionally interact with each other and the cell nucleus, behaving as an interconnected network that influence gene expression. Our work in this area is contributing to open a new paradigm of mitochondrial signal transduction – how mitochondrial networks process, integrate, and compute signals within the cytoplasm, and their implication for the vulnerability and resilience at the level of the organism.

a. Sturm G, Cardenas A, Bind MA, Horvath S, […], Hirano M, **Picard M***. Human aging DNA methylation signatures are conserved but accelerated in cultured fibroblasts. *Epigenetics* 2019. PMID: 31156022
b. Eisner V, **Picard M**, Hajnoczky G. Mitochondrial dynamics in adaptive and maladaptive cellular stress responses. *Nat Cell Biol* 2018; 20(7):655-665. PMID: 29950571
c. **Picard M**, Zhang J, […] Wallace DC. Progressive increase in mtDNA 3243A>G heteroplasmy causes abrupt transcriptional reprogramming. *PNAS*. 2014;111(38):E4033-42. PMID: 25192935
d. **Picard M**, McManus MJ, Csordás G, […], Hajnóczky G, Wallace DC. Trans-mitochondrial coordination of cristae at regulated membrane junctions. *Nat Commun* 2015; 6: 6259. PMID: 25687472

4. MITOCHONDRIAL SIGNALING and DISEASE. Extending this work to rare clinical groups of patients with mitochondrial disorders, we have integrated principles of mitochondrial genetics, epigenetics, and communication. Using this innovative perspective, my lab has defined an expanded spectrum of abnormal mitochondrial shapes and structures in biopsy samples of patients with mtDNA disorders, and developed new methods to quantify 3D mitochondrial architecture in humans and mice. We have also used machine learning to identify predictive morphological signatures of mitochondria in patients with mtDNA disorders. Combining sub-cellular molecular and imaging approaches, we also resolved the subcellular origin of mtDNA mutations and showed that mtDNA defects detrimentally expand in disease and aging through a nuclear-driven cancer-like proliferative mechanism. These findings in this rare clinical population reflect my lab's distinct line of work deciphering mitochondrial behavior, enhanced by our work with individuals with primary mitochondrial disorders, and enriched by concepts from network theory from social neuroscience.

a. Vincent AE, White K, Davey T, Philips J, […], Taylor RW, Turnbull DM, **Picard M***. Quantitative 3D mapping of the human skeletal muscle mitochondrial network in health and mtDNA disease. *Cell Rep* 2019; 26(4):996-1009. PMID: 30655224
b. Vincent AE, Rosa HS, Pabis K, Lawless C, […], Taylor RW, Turnbull DM, **Picard M***. Sub-cellular origin of mtDNA deletions in human skeletal muscle. *Annals Neurol* 2018 84(2):289-301. PMID: 30014514
c. Vincent AE, Turnbull DM, Hajnoczky G, Eisner V, **Picard M***. Mitochondrial nanotunnels. *Trends Cell Biol* 2017; 27(11):787-799. PMID: 28935166
d. **Picard M***, Hirano M. Disentangling (epi)genetic and environmental contributions to the mitochondrial 3243A>G mutation phenotype. *JAMA Neurol* 2016;73(8):1-3. PMID: 27322764

5. TRANSDISCIPLIARY SCIENCE and MENTAL HEALTH. There is a pressing need to bridge disciplinary boundaries and ask the most relevant questions that reflect the complexity of human health. Recognizing that receptors for neuroendocrine and stress mediators are located in mitochondria, that primary inherited mitochondrial disorders produce systemic symptoms strikingly similar to those of stress pathophysiology and aging, and that factors conferring protecting against chronic stress pathophysiology also have well-known beneficial effects on mitochondria, I proposed that mitochondria are positioned at the intersection of biological and psychosocial sciences. This idea has contributed to spur an inter-/transdisciplinary line of work into the role of mitochondria in mental health. I recently led an international white paper on applying these approaches to mental health and aging research, and establishing guidelines for new biomarkers.

a. Han LKM, Verhoeven JE, […], **Picard M***. Accelerating research on biological aging and mental health: Current challenges and future directions. *Psychoneuroendocrinol* 2019; 106:293-311. PMID: 31154264
b. **Picard M***. Pathways to aging: The mitochondrion at the intersection of biological and psychosocial sciences. *J Aging Res* 2011:814096. PMID: 21961065
c. Lindqvist D, Wolkowitz OM, **Picard M**, […], Reus VI, Epel ES, Mellon SH. Major depressive disorder is associated with elevated levels of circulating cell-free mitochondrial DNA, but not of leukocytes mitochondrial DNA copy number. *Neuropsychopharmacol* 2018; 43(7):1557-1564. PMID: 29453441
d. Wang Y, **Picard M**, Gu Z. Genetic evidence for elevated pathogenicity of mitochondrial DNA heteroplasmy in autism spectrum disorder. *Plos Genet* 2016; 12(10):e1006391. PMID: 27792786

Complete list of published work in MyBibliography:
www.ncbi.nlm.nih.gov/sites/myncbi/10YJmwC9Q5RA8/bibliography/40088418/public/?sort=date&direction=descending

D. Research Support

Ongoing Research Support

R01 MH119336-01 Picard (Contact), Marsland, Kaufman 5/01/19 – 2/29/24
NIMH
Transduction of Psychological Stress into Systematic Inflammation by Mitochondrial DNA Signaling
This project tests the hypothesis that circulating cell-free mtDNA release is the mechanism linking acute psychological stress and inflammation in humans.

R35 GM119793-01 Picard 9/01/16 – 8/31/21
NIGMS
Mitochondrial Stress Signal Transduction from Organelle to Organism
This project investigates the role of inter-mitochondrial communication and positioning within the cell to determine the physical basis for mitochondrial remodeling of nuclear gene expression and stress responses.

R01 HD086487-01 Tyrka 7/01/16 – 06/30/21
NIMH
Risk Profiles and Mechanisms of Disease in Maltreated Children
The goal of this project is to investigate the link between early life stress, systemic inflammation, mitochondrial dysfunction, and telomere maintenance in children 10-12 years old.
Role: Co-I (Years 4 & 5)

R01 NR016845-01 Irwin 7/01/17 – 6/30/22
NIA
Mindfulness Meditation and Insomnia in Alzheimer Disease Caregivers: Inflammatory and Biological Aging Mechanisms
This RCT investigates the effects of a mindfulness-based intervention to resolve sleep disturbances, and explore cellular mechanisms related to aging, systemic inflammation and mitochondria.
Role: Co-I

Irving Scholars Program Picard 7/01/17 – 6/30/20
Columbia CTSA Irving Institute
Profiling Mitochondrial Health to Understand Physiological Variability
This pilot project supported development of our mitochondrial phenotyping platform to understand inter-individual differences in neuroendocrine, cardiovascular, and emotional responses to psychological stress.

CU-ZI-MR-S-0002-R1 Picard 3/1/18 – 2/29/20
Zuckerman Institute
The Mitochondrial Stress, Brain Imaging, and Epigenetics Study - MiSBIE
Pilot funds to identify associations between mitochondrial phenotypes and human brain structure and function.

Completed Research Support

Faculty Research Fellowship Picard 4/01/17 – 3/31/19
Columbia Aging Center
Mitochondrial Regulation of Aging in Humans: A Transdisciplinary Investigation
Supported parallel assessments of mitochondrial dysfunction, psychological stress, and epigenetic age.

R21 MH113011 Picard 4/01/17 – 3/31/19
NINDS
Mitochondrial Regulation of Stress Reactivity in Humans
This project established feasibility of a stress reactivity protocol in patients with rare mitochondrial disorders (n=31 patients). A follow up R01 is under review.

CaMPR Phase I and II Awards Picard 4/01/16 – 05/31/17
Columbia CTSA Irving Institute (UL1TR001873)
Sub-cellular Mechanisms of Stress Perception Inside and Outside the Brain: The Role of Mitochondria
Supported the consolidation of the MiSBIE (Mitochondrial Stress, Brain Imaging, and Epigenetics) team.