BIOGRAPHICAL SKETCH

NAME: Ana Cristina Andreazza

eRA COMMONS USER NAME (credential, e.g., agency login): AANDREAZZA

POSITION TITLE: Associate Professor of Pharmacology & Toxicology and Psychiatry, University of Toronto

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of British Columbia, Vancouver, Canada, Brazil	Postdoctoral Research Fellowship	11/2008 – 10/2010 (with Dr. L.T. Young)	Mitochondrial dysfunction and mechanisms of DNA methylation
Federal University of Rio Grande do Sul, Porto Alegre, RS, Brazil	Ph.D. in Biochemistry	03/2006-04/2008 (with Dr. F. Kapczisnki)	Oxidative damage in Bipolar Disorder
University of British Columbia, Vancouver, Canada, Brazil	Research fellow	07/2007-01/2008 (with Dr. L.T. Young)	Mitochondrial Dysfunction
Federal University of Rio Grande do Sul, Porto Alegre, RS, Brazil	Master of Science	02/2005- 03/2006 (with Dr. F. Kapczsinki)	Oxidative Stress
University of Caxias do Sul, Caxias do Sul, Brazil	Pharmacist and Biochemistry	01/2000 – 12/2004	Biochemistry

A. PERSONAL STATEMENT

I am a Professor in the Departments of Pharmacology & Toxicology and Psychiatry and hold a Tier II Canada Research Chair in Molecular Pharmacology of Mood Disorders and the Thomas C. Zachos Chair in Mitochondrial Research. My research focuses on the understanding of the role of redox modulations and mitochondrial dysfunction in healthy and disease. One of my current focus is on the understanding of the role of mitochondrial function in mental illness, especially in mood disorders. As neurons depend on mitochondrial function, dysfunctional mitochondrial during neurodevelopment is expected to impact neurotransmission with potentially crucial implications for mood disorders. I am investigating the impact of mitochondrial dysfunction on neurotransmission using 3D brain organoids generated from induced pluripotent stem cells from patients with bipolar disorder and/or mitochondrial disease.

To accelerate the discovery of effective therapeutic approaches to treat mitochondrial dysfunction/disease, I founded the mitoNET.ca, which after successful fundraising and support from the University of Toronto became MITO2i – www.MITO2i.ca. The objective is to unite researchers from different medical fields with a common interest in unveiling the role of mitochondrial function and genetics in human diseases and transform mitochondrial health. Through consultation with the MITO2i community it became clear that an essential need is to identify the links between mitochondrial dysfunction and healthy and disease by bringing the voices of all scientists, clinicians, patients and advocates, industry and foundations. MITO2i was proud to launch the mitoPODCAST in June 2020 and coming soon (June 2023) the mitoVOICES. Which is aimed at building awareness for mitochondrial medicine, research and patient advocacy on topics related to mitochondrial disease and dysfunction as well as to highlight cutting-edge research. The podcast episodes are 10-15 minutes in length, accompanied by infographics, comics and will also be available in Sept 2023 with closed captioned.

Through my long standing and successful career, I have made many connections and collaborations with colleagues working in on neuropsychiatric diseases, specifically bipolar and depression and the role of mitochondria across Canada. Furthermore, through the establishment and extension of MITO2i she has also cultivated a group of world renown experts in the filed of neurodegeneration, specifically Alzheimer's and Parkinson's also exploring the changes in mitochondrial function leading to aging diseases. Under my leadership, MITO2i has funded several projects in these areas accelerating the understanding in the field of the importance of mitochondria function in the above diseases and disorders. For instance, through MITO2i, I have developed a partnership with Dr. Marcelo Cypel, Surgical Director at Ajmera Transplant Centre at University Health Network (UHN) and a Canada Research Chair in Lung Transplantation to unveil the role of mitochondrial on lung transplantation. Together, we have demonstrated the importance of maintaining mitochondrial health to preserve donor lung viability for lung transplantation. In pig experiments and ongoing clinical trials, they demonstrated that a 10°C preservation temperature (rather than the conventional 4°C) during cold ischemia results in improvement in lung function (measured by dynamic and static lung compliances, lung edema, and airway pressures); less mitochondrial injury (measured by circulating cell-free mitochondrial DNA and mtDNA oxidation); and less inflammation (measured by IL-1β and IL-8 (Ali et al., Sci Transl Med. 2021; Ali et al EbioMedicine 2022; Abdelnour-Berchtold et al , J Heart Lung Transplant. 2022)).

Finally, building on and leveraging successful multidisciplinary collaboration trough my research and MITO2i I feel that I well position to help E-mit to build a international and multidisciplinary profile. Read more about my journey.

A. POSITIONS/EMPLOYMENT:

Institution	**Position**	**Year**
University of Paris est Cretil, Foundation FondaMental University of Toronto, Department of Psychiatry	Visiting Professor	Aug, 2022 – present

University of Toronto, Department of Pharmacology	Professor	Jul, 2021 – present
University of Toronto, Department of Psychiatry	Associate Professor	Mar, 2015 – 2021
University of Toronto, Department of Pharmacology	Associate Professor	Mar, 2015 – 2021
University of Toronto, Department of Psychiatry	Assistant Professor	Mar, 2011 – Feb 2015
University of Toronto, Department of Pharmacology	Assistant Professor	Mar, 2011 – Feb 2015
University of Toronto, Institute of Medical Science	Associate Member	Dec, 2012 - present
Centre for Addiction and Mental Health	Collaborator Scientist	Nov, 2016 – present
Centre for Addiction and Mental Health	Independent Scientist	Nov, 2010 – Nov 2016

Selected Honours and Awards

April 2023 Senior Fellow, Massey College, University of Toronto
Nov 2021 Member of the Royal Society of Canada College of New Scholars
Jul 2018 Canada Top 40 Under 40 Award – The top leaders in Canada
Feb 2017 Graduate Teaching Award for Early Career Excellence in Graduate Teaching and Mentorship, Faculty of Medicine, University of Toronto
Sept 2016 CRC- Tier 2 – Canada Research Chair in Molecular Pharmacology of Mood Disorders
Mar 2014 New Investigator Award, American Society of Clinical Pharmacology (ASCP)
Dec 2013 Travel Award, American College of Neuropsychopharmacology (ACNP)
May 2011 Top Cited Article Neuroscience Letters, time period 2006-2010
Jun 2009 Lilly Young Investigator Fellowship in Bipolar Disorder, 8th International Conference of Bipolar Disorder
Jun 2009 Samuel Gershon Award for Junior Investigator, International Society of Bipolar Disorder (ISBD)

4. SELECTED ADMINISTRATIVE ACTIVITIES AND PROFESSIONAL MEMBERSHIPS

2022 – present **Scientific Steering Committee**, BD^2 – Breakthrough in bipolar disorder
2021 – present **Editorial Board**, Biological Psychiatry- GBC
2019 – present **Steering Committee Member**, Global Bipolar Cohort, , BD^2 – Breakthrough in bipolar disorder
2019 – 2021 **Conference Chair & Organizer**, MITO2019, MITO2021 – Transforming Mitochondrial Health,
2018 – present **Co-Chair** of the Women's Initiative, International Society of Bipolar Disorder
2018 – 2020 **Advisory Board**, Janssen Research & Development
2018 – 2020 **Board of Director**, International Society of Bipolar Disorder
2017 – 2020 **Advisor** for the Dauten Family Center for Bipolar Treatment Innovation at Massachusetts General Hospital
2017 – 2019 **Member**, Task Force on Biological Markers, World Federation of Societies of Biological Psychiatry
2016 – 2017 **Member**, Scientific Program Committee for International Society for Bipolar Disorders
2013 – present **Consultant**, Mayo Clinic
2011- 2012 **Member**, Research Committee of the International Society for Bipolar Disorders
2011- 2012 **Member**, Biomarkers Task Force, International Society for Bipolar Disorders
2008 – present **Faculty**, International Society for Bipolar Disorders

National

2017 – present **Scientific Director**, Mitochondrial Innovation Initiative Network
2014 – 2017 **Councillor**, Basic Science, Canadian College of Neuropsychopharmacology
2012 – present **Member**, Canadian College of Neuropsychopharmacology

Local

2019 – present **Member** of Working Group for Institutional Strategic Initiative at University of Toronto
2019-present **Advisor,** Division of Neuroscience and Clinical Translation Advisory Group
2019- present **Member**, PRiME, Precision Medicine Initiative at University of Toronto
2019 **Member** of Gender salary focus group at University of Toronto Faculty Association
2018 **Symposium Chair & Organizer**, Agilent & MitoNET – Cell metabolism and bioenergetics analysis, University of Toronto, November 08, 2018
2017 **Conference Chair & Organizer**, MITO2017 – The first mitochondrial Conference, University of Toronto, September 27-28 2017
2016 – 2019 **Member** of Decanal Promotion for the Faculty of Medicine at University of Toronto
2016 – 2018 **Member** of Executive Research and Ethics Committee for CAMH
2012 – present **Member** of Executive Steering Committee, Brain and Therapeutics Center for Addiction and Mental Health
2017 – 2019 **Member** of the Faculty of Medicine Divisional Teaching Guidelines Working Group
2017 – present **Member** of the Department of Pharmacology Partnership Committee
2018 – present **Member** of the Department of Pharmacology Promotions Committee

B. CONTRIBUTION TO SCIENCE

Significant contributions: My research publications have made significant impact on the understanding of the involvement of redox modulations (i.e oxidative stress) and mitochondrial dysfunction in mental illness, especially in mood disorder. For full list of manuscripts that I have published: https://www.ncbi.nlm.nih.gov/myncbi/ana.andreazza.1/bibliography/public/

Her most significant contributions are stated below:

1. Discovered that markers of oxidative stress are elevated in patients with bipolar disorder

Dr. Andreazza's PhD studies were one of the first to demonstrate that serum levels of antioxidant enzymes are increased in patients with bipolar disorder (BD) during the active phase of the illness (mania or depression) but not in euthymic phases (Andreazza et al, 2007a). In the same study she demonstrated that oxidative damage to lipids was increased in all phases of BD, suggesting that lipid oxidation may be a useful trait marker. During her PhD she also found that DNA is a target of oxidative damage in patients with BD with a positive correlation to the severity of symptoms of depression and mania (Andreazza et al, 2007b). These results were then replicated by her group demonstrating increased levels of 8-hydroxy-2-deoxyguanosine (8-OHdG), a marker of oxidative damage to guanosine, in BD patients compared to healthy controls. 8-OHdG levels were found to be influenced by the number of previous manic episodes and the lifetime history of psychotic symptoms (Soeiro-de-Souza et al, 2013). Investigating the role of oxidative damage to proteins, Dr. Andreazza found that patients with BD in early (within 3 years of illness onset) and late (a minimum of 10 years of illness) stages of illness have high levels of 3-nitrotyrosine while the activity of the antioxidant repair enzymes (glutathione reductase and glutathione S-transferase) were increased in late stage patients only (Andreazza et al, 2009), indicating possible nitration-induced damage in patients with BD that is present from the early stage of illness. This work then progressed towards a classification of biomarkers of neuropsychiatric disease (Davis et al, 2014), leading to Dr. Andreazza's collaboration with the World Federation of Societies of Biological Psychiatry to organize a consensus statement to help improve comparison across manuscripts by following guidelines for blood collection (Andreazza et al, 2019). Based on peripheral and central manifestations of oxidative stress Dr. Andreazza then evaluated whether serum levels of lipid oxidation might reflect the alterations in white matter or hippocampal integrity and found that lipid oxidation correlates with both a decrease of white matter integrity (Versace& Andreazza et al, 2014) and hippocampal volumes (Elvsashagen et al, 2016).

Relevant publications:

- **Andreazza AC**, Cassini C, Rosa AR, Leite MC, de Almeida LM, Nardin P, Cunha AB, Ceresér KM, Santin A, Gottfried C, Salvador M, Kapczinski F, Gonçalves CA. J Psychiatr Res. 2007; 41(6):523-9.
- (b) **Andreazza AC**, Frey BN, Erdtmann B, Salvador M, Rombaldi F, Santin A, Gonçalves CA, Kapczinski F. Psychiatry Res. 2007;153(1):27-32.
- **Andreazza AC**, Kapczinski F, Kauer-Sant'Anna M, Walz JC, Bond DJ, Gonçalves CA, Young LT, Yatham LN. J Psychiatry Neurosci. 2009; 34(4):263-71.
- Soeiro-de-Souza MG, **Andreazza AC**, Carvalho AF, Machado-Vieira R, Young LT, Moreno RA. Int J Neuropsychopharmacol. 2013;16(7):1505-12.
- Davis J, Maes M, **Andreazza A**, McGrath JJ, Tye SJ, Berk M. Mol Psychiatry.2014;20(2):152-3.
- **Andreazza AC**, Laksono I, Fernandes BS, Toben C, Lewczuk P, Riederer P, Kennedy SH, Kapogiannis D, Thibaut F, Gerlach M, et al. World J Biol Psychiatry. 2019.
- Versace A & **Andreazza AC**, Young LT, Fournier JC, Almeida JR, Stiffler RS, Lockovich JC, Aslam HA, Pollock MH, Park H, Nimgaonkar VL, Kupfer DJ, Phillips ML. EMol Psychiatry. 2014;19(2):200-8.
- Elvsåshagen T, Zuzarte P, Westlye LT, Bøen E, Josefsen D, Boye B, Hol PK, Malt UF, Young LT, **Andreazza AC**. Bipolar Disord. 2016;18(8):657-668.

2. Discovered decreased mitochondrial function and increased redox markers in post-mortem samples from patients with BD

Working with post-mortem prefrontal cortex samples from patients with BD, Dr. Andreazza demonstrated that decreased levels of NDUFS7 protein was associated with a decrease in complex I activity (Andreazza et al, 2010, 2013). Importantly, studies from post-mortem brains demonstrated downregulation of mitochondrial complex I subunits in both patients with BD and schizophrenia. Next, Dr. Andreazza's group took a fresh look at complex I microarray data and demonstrated that patients with BD have downregulation, specifically in genes involved in electron transfer in complex I. On the other hand, altered genes in schizophrenia (SCZ) were found to be scattered through complex I and exhibited both increased and decreased expression levels (Scola et al, 2013). Complex I electron transfer dysfunction is one of the major sources of reactive oxygen species production leading to oxidative damage to biomolecules. Thus, Dr. Andreazza evaluated the levels of oxidative damage to protein and found increased levels of oxidative and nitrosative damage to proteins in post-mortem prefrontal cortex from patients with BD (Andreazza et al, 2010). Dr. Andreazza, also demonstrated that myelin fraction from post-mortem prefrontal cortex have elevated levels of lipid oxidation as evidenced by increased levels of 8-isoprostane in BD and increased 4-hydroxynonenla (4-HNE) in both BD and schizophrenia. In contrast, lipid hydroperoxide (LPH) was not significantly different between groups. LPH are intermediate products of lipid oxidation which can further react to form lipid

oxidation sub-products, including 4-HNE and 8-isoprostanes. Thus, these results suggest that myelin fraction from patients with BD is associated with late stage lipid oxidation damage rather than early markers of lipid oxidation, such as LPH (Andreazza et al, 2013). More recently, Dr. Andreazza investigated 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. Her work demonstrated increases in mtDNA content in the hippocampus of patients with BD, and decreases in mtDNA oxidation in patients with BD and schizophrenia, respectively. The study also found a positive correlation between NDUFS7 and mtDNA content (ND4 and ND5) when combining brain regions, thus supporting the involvement of mitochondrial dysfunction in BD and schizophrenia (Bodenstein et al, 2020). The etiology of redox (reduction and oxidation) alterations in BD is largely unknown. Dr. Andreazza explored whether microRNAs targeting redox enzymes may have a role in BD, by examining microRNA expression in post-mortem datasets from the Stanley Neuropathology Consortium, the findings suggest that microRNAs that target redox enzymes may be good candidates for the exploration of causative factors contributing to redox alterations in BD (kim et al, 2018).

Relevant publications:

- **Andreazza AC**, Shao L, Wang JF, Young LT. Arch Gen Psychiatry. 2010;67(4):360-8.
- **Andreazza AC**, Wang JF, Salmasi F, Shao L, Young LT. J Neurochem. 2013;127(4):552-61
- Scola G, Kim HK, Young LT, **Andreazza AC**. Biological Psychiatry. 2013, 73(2) e4To-e5.
- Nunes PV, Nascimento CF, Kim HK, **Andreazza AC,** Brentani HP, Suemoto CK, Leite REP, Ferretti-Rebustini REL, Pasqualucci CA, Nitrini R, Grinberg LT, Yong LT, Jacob-Filho W, Lafer B. J Affect Disord. 2018;241:176-181.
- Kim HK, Tyryshkin K, Elmi N, Feilotter H, **Andreazza AC**. J Psychiatr Res. 2018;99:39-49.
- Bodenstein DF, Kim HK, Brown NC, Navaid B, Young LT, **Andreazza AC**. NPJ Schizophr. 2019;5(1):21.

3. Mitochondrial Dysfunction: At the Core of Psychiatric Disorders

Dysregulations in mitochondrial energetic pathways have been consistently reported across several psychiatric illnesses, Dr. Andreazza research program has contributed significantly for the growing evidence in the field. She was a guest editor on Biologic Psychiatry edition on Mitochondrial dysfunction and Psychiatric conditions (Andreazza & Nierenberg 2018, Andreazza, Duong & Young 2018). Lactate, is direct marker for mitochondrial dysfunction, have been reported elevated in brain of patients with BD (Kuong et al, 2018). Dr. Andreazza investigate the peripheral lactate levels in adolescent patients with BD and showed increased lactate levels with a positive association with circulating cell-free mitochondrial DNA, a marker of mitochondrial stress supporting that mitochondrial dysfunction are potentially present in early stages of the illness (Jeong et al 2020). Most recently, Dr. Andreazza has focus on the development of cerebral organoids from induced pluripotent stem cells (iPSCs) derived from human peripheral blood mononuclear cells to monitored mitochondrial health from the primary, reprogrammed and differentiated stages. Our results show preserved mitochondrial genetics, function and treatment responses across PBMCs to iPSCs to COs, and measurable neuronal activity in the COs. We expect our approach will serve as a model for more widespread evaluation of mitochondrial health relevant to a wide range of human diseases using readily accessible patient peripheral (PBMCs) and stem-cell derived brain tissue samples.

Relevant publications:

- Duong A, Evstratova A, Sivitilli A, Hernandez JJ, Gosio J, Wahedi A, Sondheimer N, Wrana JL, Beaulieu JM, Attisano L, **Andreazza AC**. Characterization of mitochondrial health from human peripheral blood mononuclear cells to cerebral organoids derived from induced pluripotent stem cells. Sci Rep. 2021 Feb 25; 11(1):4523
- Jeong H, Dimick MK, Sultan A, Duong A, Park SS, El Soufi El Sabbagh D, Goldstein BI, **Andreazza AC**. Peripheral biomarkers of mitochondrial dysfunction in adolescents with bipolar disorder. J Psychiatr Res. 2020;123:187-193.
- Pan AY, Ryu E, Geske JR, Zhou XY, McElroy SL, Cicek MS, Frye MA, Biernacka JM, **Andreazza AC**. The impact of sample processing on inflammatory markers in serum: Lessons learned. World J Biol Psychiatry. 2020;21(3):230-237
- **Andreazza AC**, Nierenberg AA. Mitochondrial Dysfunction: At the Core of Psychiatric Disorders? Biol Psychiatry. 2018 May 1;83(9):718-719
- **Andreazza AC**, Duong A, Young LT. Bipolar Disorder as a Mitochondrial Disease. Biol Psychiatry. 2018;83 (9):720-721.
- Kuang H, Duong A, Jeong H, Zachos K, **Andreazza AC**. Lactate in bipolar disorder: A systematic review and meta-analysis. Psychiatry Clin Neurosci. 2018;72(8):546-555.
- Bodenstein DF, Kim HK, Brown NC, Navaid B, Young LT, **Andreazza AC**. Mitochondrial DNA content and oxidation in bipolar disorder and its role across brain regions. NPJ Schizophr. 2019;5(1):21.

C. RESEARCH SUPPORT

<u>Funding relevant to this application</u>

01/2022 – 08/2024

Principal Investigator: Energy metabolism and bipolar disorder: From early detection to diagnosis and effective treatment

Co-principal: Marion Leboyer

Total funding: U$200,000

Funder: Baszucki Brain Research Foundation, Milken Institute

Project Description: Bipolar disorder (BD) is a major mood disorder characterized by cyclic periods of mania (high energy state) and depression (low energy state). There is a lack of progression in advancing novel therapeutics for BD in part due to the lack of biomarkers that could help to stratify patients through biological pathways that can guide targeted treatments, better diagnosis, management and improve disease trajectory 1-3. One of the leading hypothesis regarding BD pathology is due in part to the failure of mitochondrial function to support adequate neurotransmission and synaptic plasticity, thus affecting mood regulation, memory, and executive function4. The imbalance between energy production and its utilization - may lead to defective cell metabolism which is considered as the main culprits of metabolic syndrome, thus identifying patients with BD that suffer of mitochondrial dysfunction as an underlying biology is quintessential to improve disease trajectory; leading to intervene early to treat mitochondrial dysfunction preventing years of suffering of ineffective treatments and development of severe comorbidities such as metabolic syndrome, cardiovascular disease and diabetes.

03/2020 – 02/2025

Scientific Director -Mitochondrial Innovation Intiative - Institutional Strategic Initiative – University of Toronto

Total funding: $1,005,000.00

Funder: Intitutonal Strategic Initiative, University of Toronto

The Mitochondrial Innovation Initiative brings together a Network of researchers, clinicians, patients and advocates, academic institutions, NGOs and industry partners working together with a common mission - to transform our understanding of the role of mitochondria in human health and disease, including both rare and common chronic diseases affecting mood, metabolism, longevity and quality of life.

The relationship between mitochondrial dysfunction and severe mitochondrial disease has long been known. More recent research has established links to a broad range of neurodegenerative and metabolic disorders. This is a game-changer. Unveiling how mitochondrial dysfunction is implicated in multiple diseases will transform medical diagnoses, technologies and drug delivery systems, leading to a paradigm shift in the prevention and treatment of disease.

As mitochondrial research continues to accelerate, a lack of infrastructure for collaboration, knowledge integration and coordinated data-sharing prevents the development of a comprehensive, big-picture understanding of this crucial and emerging area of medicine that plays a role in many diseases and spans multiple disciplines, and areas of research. Together with its partners, the Mitochondrial Innovation Initiative aims to deliver supporting technologies, integrative platforms, and interdisciplinary knowledge that will lead to a paradigm shift in the way clinicians approach the diagnosis and treatment of disease and consider the potential role of mitochondrial dysfunction in multiple and prevalent medical conditions.

03/2020 – 02/2025

Thomas C. Zachos Chair in Mitochondrial Research

Total funding: $1,005,000.00

Funder: Philantropy

Supports the Mitochondiral Innovation Initative activities and the mission for Transformaing Mitochondrial Health.