BIOGRAPHICAL SKETCH

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NAME: Zachary Freyberg, M.D., Ph.D.

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

POSITION TITLE: 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	FIELD OF STUDY
Yale University, New Haven, CT	B.S.	05/1997	Molecular Biophysics & Biochemistry
Albert Einstein College of Medicine, Bronx, NY	M.S.	06/2000	Developmental & Molecular Biology
Albert Einstein College of Medicine, Bronx, NY	M.D.	06/2004	Medicine
Albert Einstein College of Medicine, Bronx, NY	Ph.D.	06/2004	Developmental & Molecular Biology
New York Presbyterian Hospital – Weill Cornell	Internship	06/2005	Internal Medicine
New York Presbyterian Hospital – Weill Cornell	Residency	06/2008	Psychiatry
Columbia University	Postdoctoral	06/2011	Research fellowship

A. Personal Statement

The overall goal of the Freyberg laboratory is to elucidate fundamental cell biological processes underlying human neuropsychiatric disorders at the molecular level – a field I have been involved in for more than 20 years. As a physician-scientist with clinical training in neurology and psychiatry, I have had direct experience working with patients struggling with bipolar disorder. Given the involvement of dopamine neurons in bipolar disorder, I have applied my basic science and clinical training to elucidate mechanisms of pre- and postsynaptic dopamine neurotransmission in this illness. My laboratory has developed novel genetic, pharmacological, and imaging tools to study vesicle dopamine loading and release as well as dopamine receptor signaling. Consequently, we have established genetic, biochemical, and cutting-edge imaging approaches to dissect the functions of dopamine neuron function and signaling in both healthy and disease contexts. Integral to these studies is the visualization of intracellular organelles and macromolecular complexes in healthy and disease states including mitochondria. Cryo-electron microscopy (**cryo-EM**) is a critical component of these imaging studies. My laboratory was one of the first to use cryo-immunoelectron microscopy, and we have since developed novel approaches in visualizing the intracellular vesicular machinery using cryo-electron microcopy and *in situ* cryo-electron tomography (**cryo-ET**). Most recently, we have applied these new cryo-imaging approaches to investigate human disease processes by visualizing the intracellular structures directly altered by disease in three dimensions at subnanometer resolution in primary cells taken from patients for the first time. In parallel, the Freyberg laboratory has been established cryo-ET approaches to intact brain tissue. We have succeeded in cryo-preservation of brain tissue from mice and non-human primates as well as in acquiring cryo-EM images of intracellular structures within cortical mouse brain tissue. As a physician-scientist and psychiatrist, I have sought to translate these powerful methods to study neuropsychiatric disease processes at cellular and molecular levels. As a first step, I have established new approaches to examine effects of mitochondrial disease-causing mutations directly on the structures of mitochondria and the affected respiratory complexes.

Recent and ongoing support I wish to highlight include:

R01 DK124219 07/17/2021-06/30/2024
Novel Dopaminergic Mechanisms of Islet Hormone Secretion and Antipsychotic Drug-Induced Metabolic Disturbances

The major goals are to establish how dopamine receptor signaling in alpha- and beta-cells regulates pancreatic islet hormone secretion and its relationships to antipsychotic drug-induced metabolic dysfunction.
Role: PI

R21 DA052419 03/01/2021-02/28/2024
CEBRA: Ultra-Fast High Resolution Imaging of Whole Mouse Brain for the Study of Drug Addiction
The goal of this award is to map the distribution of dopaminergic subpopulations activated by drugs of abuse.
Role: Contact PI

R21 AA028800 09/20/2021-08/31/2023
A Novel Role for Midbrain Glutamate Co-Transmitting Neurons in Alcohol Drinking and Motivated Behaviors
The major goal is to determine the roles of dopamine/glutamate co-transmission in alcohol drinking behaviors.
Role: MPI

PR192466 03/01/2020-02/28/2023
DoD Discovery Award, "A new i*n situ* cryo-electron microscopy approach to directly visualize mutations in mitochondrial disease"
The major goal is to establish new approaches to directly visualize the impact of mitochondrial disease-causing mutations on mitochondrial structure via cryo-electron microscopy and cryo-electron tomography.
Role: PI

B. Positions, Scientific Appointments, and Honors

Positions and Employment

2022-Present	Associate Professor of Psychiatry (Tenure Stream), Dept. of Psychiatry, University of Pittsburgh, Pittsburgh, PA
2016-2022	Assistant Professor of Psychiatry (Tenure Stream), Dept. of Psychiatry, University of Pittsburgh, Pittsburgh, PA
2016-Present	Assistant Professor of Cell Biology (Secondary Appointment), Dept. of Cell Biology, University of Pittsburgh, Pittsburgh, PA
2014-2016	Assistant Professor, Dept. of Psychiatry, Columbia University, New York, NY
2011-2014	Assistant Professor of Clinical Psychiatry, Dept. of Psychiatry, Columbia University, New York, NY
2011-2016	Research Scientist, Level VI, Grade 35, New York Psychiatric Institute Division, NY
2008-2016	Assistant Attending in Psychiatry, New York Presbyterian Hospital – Columbia Medical Center, New York, NY
2008-2011	Postdoctoral Research Fellow in Schizophrenia Research, Dept. of Psychiatry, Columbia University, New York, NY
2005-2008	Psychiatry Resident, New York Presbyterian Hospital – Weill Cornell, Payne Whitney Clinic, New York, NY
2004-2005	Internship, New York Presbyterian Hospital-Weill Cornell, New York, NY

Other Professional Experience and Service

2022-Present	Member, International College of Neuropsychopharmacology
2022-Present	Member, American Society for Clinical Investigation (ASCI)
2022-Present	Associate Member, American College of Neuropsychopharmacology
2021-Present	Topic Editor, *Frontiers in Psychiatry*
2020-Present	Reviewer, Centre for Addiction and Mental Health Discovery Fund
2020-Present	Board Member, Molecular Psychiatry Association
2019-Present	*Ad Hoc* NIH study section reviewer: Pathophysiological Basis of Mental
2019-Present	Disorders and Addictions (PMDA), NIDA Cutting Edge Basic Research Awards (CEBRA-R21) ZDA1 SXC-G
2019-Present	Member, Society of Biological Psychiatry
2018-Present	Editorial Board Member, *Cellular and Molecular Neuroscience*
2017-Present	Member, Society for Neuroscience
2017-Present	Member, Schizophrenia International Research Society
2016-Present	Member, Genetics Society of America

2016-Present	Member, International Transmembrane Transporter Society
2010-Present	Referee: *American Journal of Psychiatry*; *ACS Chemical Neuroscience*; *Journal of Affective Disorders*; *Neuropsychopharmacology*; *CNS Drugs*; *Biological Psychiatry*; *Translational Psychiatry*; *Prostaglandins, Leukotrienes and Essential Fatty Acids*; *Psychoneuroendocrinology*; *Progress in Neuro-Psychopharmacology and Biological Psychiatry*; *Schizophrenia Bulletin*; *International Journal of Neuropsychopharmacology*; *Clinical and Experimental Pharmacology and Physiology*; *Journal of Cellular and Molecular Medicine*; *Cerebral Cortex*; *Scientific Reports*; *Frontiers in Neural Circuits*; *PLoS One*; *Journal of Clinical Medicine*; *Science Advances*; *Behavioural Brain Research*; *Pharmacology Biochemistry and Behavior*; *Molecular Psychiatry*; *eLife*; *International Journal of Obesity*; *Experimental Biology and Medicine*; *Nature Metabolism*; *Journal of Physiology*; *Nature Communications*; *PNAS*
2007-2008	Member, Academy of Psychosomatic Medicine
2006-2008	Member, Steering Committee on Practice Guidelines, American Psychiatric Association
2006-2012	Member, American Psychiatric Association
2004-Present	Member, Alpha Omega Alpha Honor Society
2000-Present	Member, American Society for Cell Biology

Honors and Awards

2022	Election to membership in the American Society for Clinical Investigation
2021	Election to associate membership in American College of Neuropsychopharmacology
2021	Invited speaker, ER 2021 International Meeting, Paris, France
2021	Invited speaker, American Physical Society Annual Meeting, Virtual
2020	Invited speaker, American Society for Cell Biology, Virtual
2019	Hamilton Family Award for Basic Research in Psychiatry, Pittsburgh, PA
2019	Pilot and Feasibility Award, Pittsburgh Liver Research Center, Pittsburgh, PA
2019	A.E. Bennett Award for Basic Science, Society of Biological Psychiatry, Chicago, IL
2019	Invited Symposium Chair, Society of Biological Psychiatry Annual Meeting, Chicago, IL
2018	Invited Symposium Co-Chair & Speaker, Molecular Psychiatry Annual Meeting, HI
2018	Speaker, Senior Vice Chancellor Research Seminar, University of Pittsburgh
2017	Invited speaker, Neuroscience 2017, Washington D.C.
2017	Rising Star Research Award, Pittsburgh Foundation, Pittsburgh, PA
2016	Invited symposium speaker, Biogenic Amines and Behaviors workshop, 58th Annual *Drosophila* Research Conference, San Diego, CA
2016	Awardee of Dopamine 2016 Meeting Award, Vienna, Austria
2016	Invited Symposium Chair, Dopamine 2016 Conference, Vienna, Austria
2015	Invited speaker, Intramural Research Program seminar series, NIDA, Baltimore, MD
2013	Core Usage Funding Program Award, Columbia University, New York, NY
2013	Invited speaker, 19th International Stress and Behavior Neuroscience and Biopsychiatry Meeting, Saint Petersburg, Russia
2013	Invited speaker, Department of Genetics, Rutgers University
2012	Leon Levy Investigator Award, Columbia University, New York, NY
2012	Travel Award Winner, NIDA Frontiers in Addiction Research meeting
2012	Kopin Fellowship, The Tenth International Catecholamine Symposium
2011	Invited investigator and speaker at the 2011 Research Colloquium for Junior Investigators, American Psychiatric Association
2011	Louis V. Gerstner, Jr., Scholars Program Award, Columbia University, New York, NY
2009	“Hot Topic” speaker, 48th Annual ACNP Meeting
2007-2009	Laughlin Fellowship, American College of Psychiatrists
2006-2008	APA GlaxoSmithKline Fellowship, American Psychiatric Association
2004	Alpha Omega Alpha Honor Society
2000	American Society for Cell Biology Predoctoral Travel Award

1996 Howard Hughes Medical Institute Summer Research Fellowship
1994 Director's Commendation for Research, NINDS, NIH

C. Contributions to Science

1. We have developed new cryo-electron tomography (cryo-ET) approaches to identify the subcellular machinery of synaptic plasticity under healthy and disease conditions. By applying these methods to primary cells from patients with mitochondrial diseases, we have mapped contributions of individual proteins to mitochondrial ultrastructure in mitochondrial disease. In parallel, we used *in situ* cryo-ET imaging to discover a new organelle: a mobile form of rough endoplasmic reticulum that we termed Ribosome-Associated Vesicles (RAVs). We find RAVs coordinate activity-dependent local translation, opening the door to elucidating fundamental mechanisms responsible for synaptic plasticity in neurons.
    a. Zhu Y, Sun D, Schertel A, Ning J, Fu X, Gwo PP, Watson AM, Zanetti-Domingues LC, Martin-Fernandez ML, **Freyberg Z**, Zhang P. (2021). Serial cryoFIB/SEM reveals cytoarchitectural disruptions in Leigh syndrome patient cells. **Structure**, 29(1):82-87.e3. PMID: 33096015; PMCID: PMC7802768.
    b. Carter SD, Hampton CM, Langlois R, Melero R, Farino ZJ, Li W, Calderon MJ, Wallace CT, Tran NH, Grassucci RA, Siegmund SE, Pemberton J, Morgenstern TJ, Aguilar JI, Greenberg NL, Levy ES, Yi E, Mitchell WG, Rice WJ, Wigge C, Pilli J, George EW, Aslanoglou D, Courel M, Freyberg RJ, Javitch JA, Area-Gomez E, Shiva S, Bartolini F, Volchuk A, Murray SA, Aridor M, Fish KN, Walter P, Balla T, Fass D, Wolf SG, Watkins SC, Carazo JM, Jensen GJ, Frank J, and **Freyberg Z**. (2020). Ribosome-Associated Vesicles: a dynamic vesicular endoplasmic reticulum in secretory cells. **Science Advances**, 6(14):eaay9572. PMID: 32270040; PMCID: PMC7112762.
    c. Siegmund SE, Grassucci R, Carter SD, Barca E, Farino ZJ, Juanola-Falgarona M, Zhang P, Tanji K, Hirano M, Schon EA, Frank J, and **Freyberg Z** (2018). Three-dimensional analysis of mitochondrial crista ultrastructure in a Leigh Syndrome patient by *in situ* cryo-electron tomography. **iScience**, 6: 83-91; PMID: 30240627; PMCID: PMC6137323.
    d. Carter SD, Mageswaran SK, Farino ZJ, Maomede J, Oikonomou CM, Hope TJ, **Freyberg Z** (**Co-corresponding Author**), and Jensen GJ (2018). Distinguishing signal from autofluorescence in cryogenic correlated light and electron microscopy of mammalian cells. **Journal of Structural Biology**, 201(1):15-25. PMID: 29078993; PMCID: PMC5771259.

2. A major focus of the laboratory has been the elucidation of the mechanisms of vesicular dopamine storage/release and effects of psychostimulants on this process. We established novel optical and genetic approaches to investigate how amphetamines release dopamine from neurons *in vivo*. This led to the discovery of a new mechanism for amphetamines' actions based on the drug's actions on the vesicle monoamine transporter as a substrate-coupled H^+ antiporter. More recently, we discovered dopaminergic vesicles modify their quantal size in a pH-dependent manner in response to depolarization by relying on VGLUT-dependent loading of glutamate in dopamine vesicle during periods of dopamine neuron activity.
    a. Buck SA, Erickson-Oberg MQ, Bhatte SH, McKellar CD, Ramanathan VP, Rubin SA, **Freyberg Z**. (2022). Roles of VGLUT2 and dopamine/glutamate co-transmission in selective vulnerability to dopamine neurodegeneration. **ACS Chem Neuroscience**, 13(2):187-193. PMID: 34994539; PMCID: PMC9242677.
    b. Fiala T, Wang J, Dunn M, Šebej P, Choi SJ, Nwadibia EC, Fialova E, Martinez DM, Cheetham CE, Fogle KJ, Palladino MJ, **Freyberg Z**, Sulzer D, Sames D. (2020). Chemical targeting of voltage sensitive dyes to specific cells and molecules in the brain. **Journal of the American Chemical Society**, 142(20):9285-9301. PMID: 32395989; PMCID: PMC7750015.
    c. Aguilar JI, Dunn M, Mingote S, Karam CS, Farino ZJ, Sonders MS, Choi SJ, Grygoruk A, Zhang Y, Cela C, Choi BJ, Flores J, Freyberg RJ, McCabe BD, Mosharov EV, Krantz DE, Javitch JA, Sulzer D, Sames D, Rayport S, **Freyberg Z.** (2017). Neuronal depolarization drives increased dopamine synaptic vesicle loading via VGLUT. **Neuron**, 95(5):1074-1088. PMID: 28823729; PMCID: PMC5760215.
    d. **Freyberg Z**, Sonders MS, Aguilar JI, Hiranita T, Karam CS, Flores J, Pizzo AB, Zhang Y, Farino ZJ, Chen A, Martin CA, Kopajtic TA, Fei H, Hu G, Lin YY, Mosharov EV, McCabe BD, Freyberg RJ, Wimalasena K, Hsin LW, Sames D, Krantz DE, Katz JL, Sulzer D, Javitch JA. (2016).

Mechanisms of amphetamine action illuminated through *in vivo* optical monitoring of dopamine synaptic vesicles. **Nature Communications**, 7:10652. PMID: 26879809; PMCID: PMC4757768.

3. Our laboratory, in collaboration with Drs. Tom Hnasko and Tim Greenamyre, discovered VGLUT expression in dopamine neurons has important implications on selective dopamine neuron resilience, particularly in the contexts of age- and pesticide-induced dopamine neurodegeneration. Moreover, we found that dopamine neuron VGLUT expression is sexually dimorphic, and these sex differences are conserved across species from flies to rodents to humans. Our findings may explain the sex differences in Parkinson's disease and pave the way for new therapies to increase neuronal resilience in the setting of neurodegenerative illnesses.
    a. Steinkellner T, Conrad WS, Kovacs I, Rissman RA, Lee EB, Trojanowski JQ, **Freyberg Z**, Roy S, Luk KC, Lee VM, Hnasko TS. (2022). Dopamine neurons exhibit emergent glutamatergic identity in Parkinson's disease. **Brain**, 145(3):879-886. PMID: 35258081; PMCID: PMC9050538.
    b. Buck SA, Steinkellner T, Aslanoglou D, Villeneuve M, Bhatte SH, Childers VC, Rubin SA, De Miranda BR, O'Leary EI, Neureiter EG, Fogle KJ, Palladino MJ, Logan RW, Glausier JR, Fish KN, Lewis DA, Greenamyre JT, McCabe BD, Cheetham CEJ, Hnasko TS, **Freyberg Z**. (2021). Vesicular glutamate transporter modulates sex differences in dopamine neuron vulnerability to age-related neurodegeneration. **Aging Cell**, 20(5):e13365. PMID: 33909313; PMCID: PMC8135008.
    c. Buck SA, De Miranda BR, Logan RW, Fish KN, Greenamyre JT, **Freyberg Z**. (2021). VGLUT2 is a determinant of dopamine neuron resilience in a rotenone model of dopamine neurodegeneration. **J Neuroscience**, 41(22):4937-4947. PMID: 33893220; PMCID: PMC8260163.
    d. Steinkellner T, Zell V, Farino ZJ, Sonders MS, Villeneuve M, Freyberg RJ, Przedborski S, Lu W, **Freyberg Z**, Hnasko TS. (2018). Role for VGLUT2 in selective vulnerability of midbrain dopamine neurons. **J Clinical Investigation**, 128(2):774-788. PMID: 29337309; PMCID: PMC5785252.

4. My laboratory elucidated roles of dopamine signaling in the endocrine pancreas on hormone release. We discovered that pancreatic β-cells produce dopamine locally which functions as a local autocrine/paracrine negative regulator of insulin secretion. More recently, we have also begun studying dopamine signaling in α-cells, showing that α-cells similarly produce their own dopamine to control glucagon secretion. Our work is among the first to examine if blockade of peripheral dopamine receptors in α- and β-cells plays an important role in the development of metabolic disturbances produced by antipsychotic drugs.
    a. **Freyberg Z**, Gittes GK. (2023). Roles of pancreatic islet catecholamine neurotransmitters in glycemic control and in antipsychotic drug-induced dysglycemia. **Diabetes**, 72(1):3-15. PMID: 36538602.
    b. Aslanoglou D, Bertera S, Friggeri L, Sanchez-Soto M, Lee J, Xue X, Logan RW, Lane JR, Yechoor VK, McCormick PJ, Meiler J, Free RB, Sibley DR, Bottino R, **Freyberg Z**. (2022). Dual pancreatic adrenergic and dopaminergic signaling as a therapeutic target of bromocriptine. **iScience**, 25(8):104771. PMID: 35982797. PMCID: PMC9379584.
    c. Aslanoglou D, Bertera S, Sanchez-Soto M, Free RB, Lee J, Zong W, Xue X, Shrestha S, Brissova M, Logan RW, Wollheim CB, Trucco M, Yechoor VK, Sibley DR, Bottino R, **Freyberg Z**. (2021). Dopamine regulates pancreatic glucagon and insulin secretion via adrenergic and dopaminergic receptors. **Translational Psychiatry**, 11(1):59. PMID: 33589583; PMCID: PMC7884786.
    d. Farino ZJ, Morgenstern TJ, Maffei A, Quick M, De Solis A, Wiriyasermkul P, Freyberg RJ, Aslanoglou D, Sorisio D, Inbar B, Free R, Donthamsetti P, Mosharov E, Kellendonk C, Schwartz GJ, Sibley D, Schmauss C, Zeltser L, Moore H, Harris PE, Javitch JA, and **Freyberg Z**. (2020). New roles for dopamine D_2 and D_3 receptors in pancreatic beta cell insulin secretion. **Molecular Psychiatry**, 25(9): 2070-2085. PMID: 30626912; PMCID: PMC6616020.

Complete list of published works in MyBibliography:
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