Division of Molecular Therapeutics

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Overview

Research in the Division of Molecular Therapeutics focuses on understanding molecular and cellular processes that underlie behavior, with an emphasis on existing or novel targets for therapeutic intervention in psychiatric disorders. The Division has a specialized expertise in dopaminergic signaling, midbrain dopamine neurons. These neurons are thought to play an important role in the rewarding effects of abused drugs, as well as to figure importantly in the pathogenesis of schizophrenia. Projects are multidisciplinary and range from studies on the biochemical and biophysical characterization of basic molecular processes that underlie drug responses, to cellular physiology, and to behavior.

Current Research

Cognitive deficits are central to schizophrenia but the underlying mechanisms still remain unclear. Imaging studies performed in patients point to decreased activity in the medio-dorsal thalamus (MD) and reduced functional connectivity between the MD and prefrontal cortex (PFC) as candidate mechanisms. However, a causal link is still missing. The **Kellendonk** lab used a pharmacogenetic approach in mice to diminish MD neuron activity and the behavioral and physiological consequences and found that a subtle decrease in MD activity is sufficient to trigger selective impairments in prefrontal-dependent cognitive tasks. *In vivo* recordings in behaving animals revealed that MD-PFC beta-range synchrony is enhanced during acquisition and performance of a working memory task. Decreasing MD activity interfered with this task-dependent modulation of MD-PFC synchrony, which correlated with impaired working memory. These findings suggest that altered MD activity is sufficient to disrupt prefrontal-dependent cognitive behaviors, and could contribute to the cognitive symptoms observed in schizophrenia patients.

The **Rayport** lab is studying the midbrain dopamine neurons that are thought to mediate the rewarding effects of abused drugs as well as to figure prominently in the pathophysiology of schizophrenia. They have shown in a coordinated series of molecular, physiological and morphological studies that dopamine neurons use glutamate as a co-transmitter. This unique signal may play an important role in encoding salience during reward learning, and may be an important substrate for enduring physiological and pathological changes in dopamine system function. They are now taking a functional connectomes approach to dissecting the synaptic actions of dopamine neurons neurons using optogenetics. They are

implementing genetic strategies in mice, in collaboration with Holly Moore (Integrative Neuroscience), to modulate tonic and phasic dopamine neuron activity in order to evaluate how dopamine neuron activity may be altered in schizophrenia. In a second line of work, Rayport and colleagues have shown that mice with a genetic reduction in glutaminase (gene GLS1) manifest a schizophrenia resilience profile. They are now asking two questions: (1) does a knockdown of GLS1 in adulthood generate the same resilience profile using a strategy they term Genetic Pharmacotherapy, and (2) whether a restricted knockdown of GLS1 in the hippocampus, cortex or in dopamine neurons generate the resilience profile using a tissue-specific promoter strategy.

Using a mouse model, the **Schmauss** lab discovered a novel epigenetic mark of early life stress exposure that influences emotional and executive cognitive behavior in adulthood as well as the responsiveness to antidepressant treatment. This epigenetic mark is propagated to the next generation of mothers (but not fathers) exposed to early life stress. This transmission is germ-line independent, mediated by maternal behavior during postnatal care of the offspring, and can be reversed with drugs that erase the epigenetic mark in the mother. These findings are of significance for our understanding of the trans-generational effects of maternal psychopathology.

The **Sulzer** lab is focused on studies of basal ganglia synapses as well as elucidating pathophysiological mechanism in these systems. The synaptic studies are becoming increasingly focused on determining the rules by which particular synapses are selected by activity and neurotransmitter systems, so that organisms can learn new behaviors and decide between responses. The disease-oriented studies attempt to elucidate causes of addiction, Parkinson's and Huntington's diseases, schizophrenia, and autism.

Research in the **Javitch** laboratory is aimed at understanding the structure, function and regulation of G protein-coupled receptors and neurotransmitter transporters using biochemical and biophysical approaches. Genetically engineered flies and mice are also being used to translate our molecular studies to the behavioral level. Dr. Zachary **Freyberg** has begun examining the roles of dopamine and dopamine receptors in antipsychotic drug-induced metabolic disturbances using tissue-selective dopamine receptor knockout mice and insulin-releasing pancreatic islet cells. He has succeeded in visualizing effects of dopamine and dopamine receptors on dynamics of glucose-stimulated release in insulin-releasing pancreatic islet cells via biochemical and light microscopic techniques. The ultimate goal of this work is to facilitate further characterization of antipsychotic drugs' molecular actions in brain and metabolism and move us towards clinically effective treatments with greater specificity and fewer side effects. Initial studies in this project were recently published in *Molecular Endocrinology*. Dr. Matthias **Quick** is focusing on the relationship of the structure and function ofneurotransmitter:sodium symporters (NSS) and other membrane

transport proteins with special emphasis on the dynamics that are associated with the coupling of Na+ and substrate transport.

Education & Training

Sheng-Han Kuo received the Lucien Cote Award from the Parkinson's Disease Foundation, and the Foundation Award from the American Academy of Neurology for his work on Parkinson's Disease. He received a 20 on his K01 and the award is expected.

Guomei Tang received a K01 for her work on autism.

Daniela Hernandez received her PhD and published a new paper in Neuron introducing the role of autophagy in presynaptic plasticity.

Dr. Freyberg is currently mentoring a master's student in the master's program affiliated with the Institute of Human Nutrition. Additionally, two undergraduate students from Stern College for Women of Yeshiva University are working under Dr. Freyberg's supervision.

Post-doctoral fellow, Maxime Cazorla successfully competed for the ANR-RPDOC grant of the ANR (Agence Nationale de la Recherche) in France and returned October 2012 to France (430,404 EUR, supplemented with 942,202 EUR from CNRS and INSERM)

Dr. Rayport is mentoring SURF/AMGEN undergraduate students and a Heschel High School Science Honors student as well as a new Schizophrenia Research Fellow, Abigail Kalmbach, PhD.

Didactic: G4100 graduate course in Neuroscience: *Biology of Neurologic and Psychiatric Disorders* (Rayport, course director with René Hen and Scott Small)

Honors & Awards

Freyberg:
Kopin Fellowship, The Tenth International Catecholamine Symposium
Selection as Early Career Investigator presenter and Travel Award Winner at NIDA Frontiers in Addiction Research meeting
Leon Levy Investigator Award, Columbia University, New York, NY
Invited Psychiatric Grand Rounds presenter, Maimonides Hospital, Brooklyn, NY
Selection as a speaker at the 19th International Stress and Behavior Neuroscience and Biopsychiatry meeting, Saint Petersburg, Russia

Caline **Karam** received a NARSAD Young Investigator Award**:** *A high-throughput genetic screen to identify novel modulators of presynaptic dopamine stores in vivo*

Kellendonk:

Forest Research Institute (Kellendonk, PI) 01/08/2013-12/31/2013
FRI RGH-MD-45
"Further behavioral studies in dopamine receptor over-expressing mice"
The goal is study the consequences of the D2/D3 partial agonists aripriprazole and cariprazine on motivational behavior in D2R over-expressing and wild type mice.

Susana **Mingote** received a NARSAD Young Investigator Award: *Does Dopamine Neuron Glutamate Signaling Play a Crucial Role in the Transition to Addiction?*

Quick:

Invited lectures:

June 15, 2012: Department of Biology I, Ludwig-Maximilians-University, Martinsried, Germany.
June 21, 2012: The Max Planck Institute of Biophysics, Dept. of Structural Biology, Frankfurt, Germany.
August 6-15, 2012: Aarhus University - Summer school course ”Structure and function of membrane transporters” , Aarhus, Denmark
September 17, 2012: 17th European Bioenergetics Conference EBEC, University of Freiburg, Germany EBEC
November 16, 2013: Binghamton University, Dept. of Chemistry

Schmauss:

Appointed Vice Chair of the university-wide Columbia IACUC on January 1, 2013.

September 2012: IR CU12070-033823: International Invention Report filed through Columbia University for a novel biomarker capable of predicting antidepressant efficacy (Inventor: C.S.)

Sulzer:

2012 Plenary talk, Monitoring Molecules in Neuroscience, Imperial College London
2012 Keynote Lecture in Cellular Neuroscience, Yale University
2012 Frontiers of Neuroscience, Emory University
2012- Board of Scientific Directors, Parkinson’s Disease Foundation
2012-2017 PPG with UCSF, PI Project 1, *Presynaptic plasticity of vesicular dopamine release*, NIDA, (this PPG is a collaboration with U.C.S.F.), $800,000 for Sulzer lab
2012-2015 DOD, *Altered astrocyte-neuron interactions and epileptogenesis in tuberous sclerosis disorder*, $701,548, PI
2012-2014 NINDS Udall supplement for postdoc (Jose Lizardi-Ortiz),

~$100,000
2012-2013 Lucien Cote Award for postdoc, Sheng-Han Kuo, $60,000
2012-2015 JPB Foundation, *Mechanisms of substantia nigra neuronal death in Parkinson's disease*, $2,100,000

Javitch:

2012-17 NIDA Senior Scientist Award K05, Molecular Determinants for the Action of Psychostimulants.

2012- Scientific Advisory Board, Hope for Depression Research Foundation

G-Protein Signaling Workshop, Rockefeller University, New York, NY
Gordon Research Conference, Mechanisms of Membrane Transport, LeDiablerets, Switzerland.
Xth Annual Catecholamine Symposium, Asilomar, CA.
Biophysical Society, Signaling Dynamics of Membrane Proteins in Living Cells, Philadelphia, PA.
UCSF Seminar, San Francisco, CA.
UCLA Seminar, Los Angeles, CA.
Duke Seminar, Durham, NC.
University of Texas San Antonio Seminar, San Antonio, CA

Publications (Selected)

Levin, EL, Cao, Y, Enkavi, G, Quick, M, Pan, Y, Tajkhorshid, E, Zhou, M: Structure and permeation mechanism of a mammalian urea transporter. *Proc. Natl. Acad. Sci. U.S.A.* 2012; 109:11194-11199

Khafizov, K, Perez, C, Koshy, C, Quick, M, Fendler, K, Ziegler C, Forrest, LR: Identification of the sodium binding sites in the sodium-coupled betaine transporter BetP. *Proc. Natl. Acad. Sci. U.S.A.* 2012; 109:E3035-3044

S. Parnaudeau, P.K. O'Neill1, S. Bolkan, R.D. Ward, A.I. Abbas, B.L. Roth, P. Balsam, J.A. Gordon, C. Kellendonk (2013) Inhibition of medio-dorsal thalamus disrupts thalamo-frontal connectivity and cognition *Neuron* 77:1151–1162

Zimnisky R, Chang, G., Gyertyán, I., Kiss, B., Adham, N., and Schmauss, C. (2013). Carprazine, a dopamine D3-receptor-preferring partial agonist, blocks PCP-induced impairment of working memory, attention set-shifting, and recognition memory in the mouse. *Psychopharmacology* 226: 91-100.

Bae N, Wang Y, Li L, Rayport S, Lubec G (2013) Network of brain protein level changes in glutaminase deficient fetal mice. J Proteomics 80:236–249.

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Mihali A, Subramani S, Kaunitz G, Rayport S, Gaisler-Salomon I (2012) Modeling resilience to schizophrenia in genetically modified mice: a novel approach to drug discovery. Expert Rev Neurother 12:785–799.

Daniela Hernandez, Ciara A. Torres, Wanda Setlik, Carolina Cebrián, Eugene V. Mosharov, Guomei Tang, Hsiao-Chun Cheng, Nikolai Kholodilov, Olga Yarygina, Robert E. Burke, Michael Gershon, David Sulzer (2012). Regulation of presynaptic neurotransmission by macroautophagy. Neuron, 74:277-284.

Anzalone A*, Lizardi-Ortiz* JE, Ramos M, De Mei C, Hopf FW, Iaccarino C, Halbout B, Jacobsen J, Kinoshita C, Welter M, Caron MG, Bonci A, Sulzer D, Borrelli E. (2012) Dual Control of Dopamine Synthesis and Release by Presynaptic and Postsynaptic Dopamine D2 Receptors. Journal of Neuroscience, 32:9023-9034. *co-first author

Conrad KL, Davis AR, Silberman Y, Sheffler DJ, Shields AD, Saleh SA, Sen N, Matthies HJ, Javitch JA, Lindsley CW, Winder DG. Yohimbine depresses excitatory transmission in BNST and impairs extinction of cocaine place preference through orexin-dependent, norepinephrine-independent processes. *Neuropsychopharmacology,* [Epub ahead of print] (2012).

Newman AH, Beuming T, Banala AK, Donthamsetti P, Pongetti K, Labounty A, Levy B, Cao J, Michino M, Luedtke RR, Javitch JA, Shi L. Molecular determinants of selectivity and efficacy at the dopamine D3 receptor. *J Med Chem*. 55:6689-99 (2012).

Geng Y, Xiong D, Mosyak L, Malito DL, Kniazeff J, Chen Y, Burmakina S, Quick M, Bush M, Javitch JA, Pin JP, Fan QR. Structure and functional interaction of the extracellular domain of human GABA(B) receptor GBR2. *Nat Neurosci.* 15:970-8 (2012).

Pizzo AB, Karam CS, Zhang Y, Yano H, Freyberg RJ, Karam DS, Freyberg Z, Yamamoto A, McCabe BD, Javitch JA. The membrane raft protein Flotillin-1 is essential in dopamine neurons for amphetamine-induced behavior in Drosophila. *Mol Psychiatry*. [Epub ahead of print] (2012).

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Negri A, Rives ML, Caspers MJ, Prisinzano TE, **Javitch** JA, Filizola M. Discovery of a Novel Selective Kappa-Opioid Receptor Agonist Using Crystal Structure-Based Virtual Screening. J Chem Inf Model. 2013 Mar 13. [Epub ahead of print] PMID: 23461591

Divisional Highlights

Zachary Freyberg - Leon Levy Investigator Award, Columbia University, New York, NY

Susana Mingote and Caline Karam received NARSAD Young Investigator Awards.

Claudia Schmauss - appointed Vice Chair of the university-wide Columbia IACUC

David Sulzer - PPG with UCSF, PI Project 1, *Presynaptic plasticity of vesicular dopamine release*, NIDA, (this PPG is a collaboration with U.C.S.F.), $800,000 for Sulzer lab

Jonathan Javitch - NIDA Senior Scientist Award K05, Molecular Determinants for the Action of Psychostimulants.

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