

## **Division of Molecular Therapeutics**

### **JONATHAN A. JAVITCH, M.D, PH.D., DIRECTOR**

#### **1. Highlights**

Dr. Javitch was appointed as Scientific Director of the Lieber Center for Schizophrenia Research and Treatment at Columbia University.

#### **2. Staff**

Jonathan A. Javitch, M.D., Ph.D., Research Scientist V  
Mahalaxmi Aburi, Ph.D., Assistant Research Scientist I  
Lynn Chung, Technician B  
Concetta Dipace, Ph.D., Assistant Research Scientist II  
Douglas Drake, Project Administrator  
Lihua Duan, Staff Associate  
Wen Guo, Ph.D., Research Scientist I  
Yang Han, Ph.D., Assistant Research Scientist I  
Hector Herrera, Research Support Assistant III  
Michaela Kralikova, Ph.D., Postdoctoral Research Scientist  
Andrea Pizzo, Ph.D., Assistant Research Scientist I  
Matthias Quick, Ph.D., Research Associate  
Namita Sen, Ph.D., Research Scientist II  
Mark Sonders, Ph.D., Research Scientist II  
Eneko Urizar, Ph.D., Postdoctoral Research Scientist  
Yongfang Zhao, Ph.D., Postdoctoral Research Scientist

#### **3. Current Research**

Dr. Javitch's research focuses on understanding the structure, function, and regulation of G-protein coupled receptors and neurotransmitter transporters. His group has been mapping the transmembrane interfaces of dopamine D2 receptor homo-oligomers in the plasma membrane and has identified conformational changes at the interface that determine receptor activation. His group has demonstrated that phosphorylation of the amino-terminus of the dopamine transporter is essential for amphetamine-mediated reverse transport of dopamine, and he and his collaborators have begun to elucidate the molecular mechanisms that govern this regulation. He is now pursuing studies in knock-in mice and transgenic flies to explore these mechanisms in a physiological context. His laboratory is also taking direct structural approaches to studying the structure and dynamics of bacterial transporter homologues of the human neurotransmitter transporters.

#### **4. Awards and Honors**

Dr. Javitch was appointed as a member of the Scientific Council of NARSAD and as Chairperson of the NIH Biophysics of Neural Systems study section.

## 5. Publications

Kahlig, K.M., Lute, B.J., Wei, Y., Loland, C.J., Gether, U., **Javitch, J.A.**, Galli, A. Regulation of Dopamine Transporter Trafficking by Intracellular Amphetamine. *Mol Pharmacol.*70:542-8 (2006).

Fog, J.U., Khoshbouei, H., Holy, M., Owen, W.A., Bjerggaard, C., Sen, N., Nikandrova, Y., Bowton, E., McMahon, D.G., Colbran, R.J., Daws, L.C., Sitte, H.H., **Javitch, J.A.**, Galli, A., Gether, U. Calmodulin kinase II interacts with the dopamine transporter C-terminus to regulate amphetamine-induced reverse transport, *Neuron* 51: 417-429 (2006).

Quick, M., Yano, H., Goldberg, N., Duan, L., Beuming, T., Shi, L., Weinstein, H., **Javitch, J.A.** State-dependent conformations of the translocation pathway in the tyrosine transporter Tyt1, a novel neurotransmitter: sodium symporter, *J. Biol. Chem.* 281:26444-54 (2006).

Beuming, T., Shi, L., **Javitch, J.A.**, Weinstein, H. A comprehensive structure-based alignment of prokaryotic and eukaryotic neurotransmitter/Na<sup>+</sup> symporters (NSS) aids in the use of the LeuT structure to probe NSS structure and function, *Mol. Pharmacol.*70:1630-42, (2006).

Wei, Y., Williams, J., **Javitch, J.A.**, Galli, A., Saunders, C. Dopamine transporter activity mediates amphetamine-induced inhibition of Akt through a CamKII dependent mechanism, *Mol Pharmacol.* 71:835-42 (2007).

Bolan, E.A., Kivell, B., Jaligam, V., Oz, M., Jayanthi, L.D., Han, Y., Sen, N., Urizar, E., Gomes, I., Devi, L.A., Ramamoorthy, S., **Javitch, J.A.**, Zapata, A., Shippenberg, T.S. D2 Receptors Regulate Dopamine Transporter Function Via an ERK 1/2-Dependent and PI3 Kinase-Independent Mechanism, *Mol Pharmacol.* Jan. 31 e-pub (2007).

Quick, M. **Javitch, J.A.** Monitoring the activity of membrane transport proteins in detergent-solubilized form, *Proc. Natl. Acad. Sci. USA.* 104: 3603-3608 (2007).

Skrabanek, L., Murcia, M., Bouvier, M., Devi, L., George, S.R., Lohse, M.J., Milligan, G., Neubig, R., Palczewski, K., Parmentier, M., Pin, J.P., Vriend, G., **Javitch, J.A.**, Campagne, F., Filizola, M. Requirements and ontology for a G protein-coupled receptor oligomerization knowledge base. *BMC Bioinformatics.* 8:177 (2007).

Shi, L., **Javitch, J.A.** A role for information collection, management, and integration in structure-function studies of G-protein coupled receptors. *Curr Pharm Des.* 12:1771-83 (2006).

Urban, J.D., Clarke, W.P., von Zastrow, M., Nichols, D.E., Kobilka, B.K., Weinstein, H., **Javitch, J.A.**, Roth, B.L., Christopoulos, A., Sexton, P., Miller, K., Spedding, M.,

Mailman, R.B. Functional selectivity and classical concepts of quantitative pharmacology. *J Pharmacol Exp Ther.* 320:1-13 (2007).

## **STEPHEN RAYPORT, M.D., PH.D.**

### **1. Highlights**

In further studies of dopamine neuron glutamatergic synaptic transmission, Rayport and colleagues have shown that fast dopamine neuron signaling is mediated by glutamate exclusively. Co-released dopamine modulates the glutamatergic signal via counterbalanced D2- mediated presynaptic inhibition and D1-mediated postsynaptic facilitation. At burst-firing frequencies, postsynaptic facilitation dominates and dopamine augments the glutamatergic signal. In this way, dopamine neuron glutamate cotransmission provides for fast signaling of salience information, enhanced by dopamine corelease when dopamine neurons fire in burst mode.

On the postsynaptic side, they have shown that dopamine receptors are positioned on the presynaptic terminals of medium-spiny neurons in the nucleus accumbens where they potently modulate GABAergic synaptic transmission. They have gone on to show that the distribution of receptors is heterogeneous, suggesting that medium-spiny neurons can traffic dopamine receptors to individual synapses selectively. This work identifies a potential substrate for neuroplastic modulation of information processing in the area.

In a hypoglutamatergic mouse model, they have shown paradoxically that knockdown of the glutamate-synthesizing enzyme phosphate-activated glutaminase (GLS1) produces a mouse with a phenotype of schizophrenia resilience, suggesting a novel target for the pharmacotherapy of schizophrenia.

### **2. Staff**

Stephen Rayport, M.D., Ph.D., Research Psychiatrist II  
Won Yong Choi, Ph.D., Research Scientist I  
Nao Chuhma, M.D., Ph.D., Research Scientist III  
Inna Gaisler-Salomon, Ph.D., Research Scientist I  
Ningning Guo, Ph.D., Research Scientist II  
Susana Mingote, Ph.D., Research Scientist I  
Takeo Mizuno, M.D., Ph.D., Research Scientist I  
Yvonne Wang, hourly employee (Barnard Class of 2010)

**3. Current Research** – See Highlights.

**4. Awards and Honors** – None

**5. Publications**

Geldwert D, Norris JM, Feldman IG, Schulman JJ, Joyce MP, **Rayport S** (2006) Dopamine presynaptically and heterogeneously modulates nucleus accumbens medium-spiny neuron GABA synapses in vitro. *BMC Neurosci* 7:53.

Jiang M, Guo W, Scheiren I, Narendran R, Javitch J, **Rayport S**, Laruelle M (2006) Agonist-mediated internalization of dopamine D2 receptors does not appear to mediate the decrease in benzamides binding potential observed after dopamine surge. *Neuroimage* 31:T32.

Mizuno T, Schmauss C, **Rayport S** (2007) Distinct roles of presynaptic dopamine receptors in the differential modulation of the intrinsic synapses of medium-spiny neurons in the nucleus accumbens. *BMC Neurosci* 8:8.

Stahl RGW, **Rayport S**, Sulzer D (2007) Amperometric detection of dopamine exocytosis from synaptic terminals. In: *Electrochemical Methods for Neuroscience* (Michael AC, Borland LM, eds), pp 337-352. Boca Raton: Taylor & Francis.

## **CLAUDIA SCHMAUSS, M.D.**

### **1. Highlights**

Serotonin 2C receptors are implicated in the control of mood. Previous research in the Schmauss lab has shown that subjects with major depression exhibit an abnormally increased expression of prefrontal cortical 5-HT<sub>2C</sub> receptors that result from RNA editing and that have reduced functions. In a recent study (Bhansali et al., 2007), the Schmauss lab showed that the spontaneously anxious inbred mouse strain Balb/c develops a similar alteration in 5-HT<sub>2C</sub> receptor expression when such mice were exposed to early life stress. These studies highlight the significance of an interaction between background genes that confer susceptibility for developing depression and a stressful environment, and they have begun to unravel the molecular mechanisms that mediate changes in 5-HT<sub>2C</sub> receptor expression and that are responsive to antidepressant drug treatment of the SSRI type.

### **2. Staff**

Claudia Schmauss, M.D., Research Scientist V  
Sylvia Navailles, Ph.D., Research Scientist II  
Jane Dunning, Ph.D., Research Scientist II  
Deirdre DeSteno, M.S.; Ph.D./Graduate Student in Pharmacology at Columbia University

### **3. Current Research**

Project 1: Molecular and behavioral studies on the genetic and environmental regulation of (1) RNA editing and (2) expression of functionally related genes.

Project 2: Behavioral and anatomic studies on the role of adult hippocampal neurogenesis in the expression of depression-like behavioral phenotypes and antidepressant drug actions in genetically different inbred strains of mice.

Project 3: Behavioral and anatomic studies on gene activation mediated by regulatory transcription factors of the immediate early gene family in neuronal networks that support attention and working memory in the mouse.

#### **4. Awards and Honors**

No new awards during the last year.

#### **5. Publications**

Li, Z.S., **Schmauss, C.** Cuenca, A., Ratcliffe E., & Gershon, M.D. (2006). Physiological modulation of intestinal motility by enteric dopamine neurons and the D2 receptor. *J. Neurosci.* **26**: 2798-2807.

Bhansali, P., Dunning, J., Singer, S.E., David, L., & **Schmauss, C.** (2007). Early life stress alters adult serotonin 2C receptor pre-mRNA editing and expression of the alpha subunit of heterotrimeric G protein Gq. *J. Neurosci.* **27**: 1467-1473

### **DAVID SULZER, M.D.**

#### **1. Highlights**

The Sulzer lab received a \$1.5M grant from the Picower Foundation and a competitive renewal of an R01 from NIDA.

#### **2. Staff**

David Sulzer, M.D., Research Scientist V  
Candace Bernard, Research Assistant  
Daniela Pereira, Ph.D., Postdoctoral Research Scientist  
Eugene V. Mosharov, Ph.D., Associate Research Scientist  
Yvonne E. Schmitz, Ph.D., Associate Research Scientist  
Zsolt Talloczy, Ph.D., Associate Research Scientist  
Hui Zhang, Ph.D., Associate Research Scientist  
Daniela Hernandez; Ph.D. student  
Yelena Kanter, Technician B  
Rosa de Vries, rotating foreign M.D./Ph.D. student

#### **3. Current Research**

Dr. Sulzer is PI of a NIDA multi-departmental T32 training grant devoted to basic neuroscience research. The specific focus of the program is to elucidate basic neural mechanisms associated with drugs of abuse. Nineteen faculty from basic and clinical departments with interest and expertise in this area act as mentors. While Columbia University has a training grant to provide support for clinical research in drug abuse, there has never been a training program in basic research in drug abuse.

#### 4. Awards and Honors

Plenary talk, *50 Years of Dopamine*, Gothenburg, Sweden, May, 2007.

#### 5. Publications

Larsen, K.E., Benn, S.C., Chian R.J., Ay, I., Celia, S.A., Remington, M.P., Bejarano, M., Liu, M., Doss, J., Carmillo, P. Sah, D., Phillips, K.A., **Sulzer, D.**, Pepinsky, R.B., Fishman, P.S., Brown, R.H., Francis, J.W. (2006) A glial cell line-derived neurotrophic factor (GDNF):tetanus toxin fragment C protein conjugate improves delivery of GDNF to spinal cord motor neurons. *Brain Res*, 1120:1-12.

Mosharov, E., Staal, R.G.W., Bov, J., Hananiya, A., Markov, D., Poulsen, N., Larsen, K.E., Troyer, M.D., Edwards, R.H., Przedborski, S., **Sulzer, D.** (2006) Alpha-synuclein overexpression permeabilizes secretory vesicles and increases cytosolic catecholamine. *J Neurosci*, 26:9304-93311.

Larsen, K.E., Schmitz, Y. Troyer, M., Mosharov, E., Dietrich, P., Savalle, M., Edwards, R. H., Stefanis, L., **Sulzer, D.** (2006) Alpha-synuclein overexpression in PC12 and chromaffin cells impairs catecholamine release by interfering with a late step in exocytosis. *J Neurosci.*, 26: 11915-11922.

**Sulzer, D.** Multiple hit hypotheses for dopamine neuron loss in Parkinson's Disease (2007). Invited review special issue, *50 Years of Dopamine Trends in Neuroscience*, 30:244-250.

Schmitz, Y. and **Sulzer, D.** (2007) Parkinson's disease: return of an old prime suspect. invited review, *Neuron* 55:8-10.

Staal, R.G.W., Rayport, S., **Sulzer, D.**, (2007). Amperometric detection of dopamine exocytosis from synaptic terminals. *In Electrochemical Methods in Neuroscience* (edited Adrian Michael) in the series Methods and New Frontiers In Neuroscience (edited M. Nicolelis and S.A. Simon) CRC Press, pages 337-352.