

## **Division of Translational Imaging**

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### **Overview**

The mission of the Division is to use imaging to uncover the neural basis of psychiatric disorders and aid in drug development.

The area of research of the Division of Translational Imaging (DTI) at NYSPI is the development of novel tools and techniques to study neurotransmission in the living human brain, and the application of these techniques to clinical studies to unravel chemical imbalances associated with severe mental illnesses and drug addiction. Molecular imaging techniques based on Positron Emission Tomography (PET) are the main methods developed and used in the Division. The imaging approach has a translational emphasis, using imaging to identify phenotypes that can be tested in animal models or vice versa using models derived from preclinical knowledge to be tested in clinical populations. Development of new imaging techniques includes design of new radiotracers (organic synthesis, chemical structure-activity relationship, in vitro evaluation, experiments in rodents and primates, dosimetry and toxicology evaluation, filing of IND, phase 1 and 2 studies in humans), as well as development of new imaging paradigms based on pharmacological challenges, cognitive tasks or electromagnetic challenges to measure responsiveness of neurotransmitter systems.

Clinical investigations within the Division focus on schizophrenia (SCZ), cannabis dependence and comorbidity with schizophrenia, MDMA dependence, design of paradigms to assess dopamine release in response to alcohol challenge and reward related tasks, identification of biomarkers for disease prevention or drug discovery and development.

Additionally, the Division performs imaging studies in collaboration with other investigators who specialize in the study of various disorders: anxiety disorders (Dr. Simpson), mood disorders (Dr. Schneier), autism (Dr. Hollander from Mt Sinai), personality disorders (Dr. Siever from Mt Sinai) and alcoholism (Dr. Krystal from Yale).

### **Staff**

Anissa Abi-Dargham MD, Psychiatrist Research II  
Balu Easwaramoorthy, PhD. Research Scientist IV  
Roberto Gil, MD, Research Scientist  
Lawrence Kegeles MD PhD, Research Scientist 6

## Current Research

**Assess cortical and striatal dysregulation in SCZ:** Striatal DA excess is a well established phenotype in SCZ, but little is known about DA dysfunction in the cortex, in part because assessment of cortical DA release has not been feasible so far. Researchers in the Division now have new data suggesting its feasibility with the high affinity D2/3 radiotracer [11C]FLB 457 combined with the D-amphetamine challenge. The study comparing patients with schizophrenia and healthy controls matched for age, gender, ethnicity, smoking, parental socioeconomic status and catechol-O-methyltransferase (COMT) genotype has begun. The Division's researchers postulate that cortical DA will be decreased in dorsolateral prefrontal cortex in SCZ. This will provide the first and most direct examination currently possible of the capacity for DA release in DLPFC in SCZ. This knowledge is essential as a first step for developing treatments of cognitive dysfunction in SCZ.

**Study comorbidity: SCZ and cannabis dependence:** The group has studied striatal DA transmission across many disease categories. It has been observed that DA transmission is predominantly blunted in the ventral striatum (VST) in alcoholism (43) similarly to cocaine dependence. On the other hand, in SCZ, DA transmission is increased in the associative striatum, and, more specifically, in the precommissural dorsal caudate (preDCA).

The intriguing next question the Division is addressing now relates to dual diagnosis patients suffering from both SCZ and addiction, and in particular those suffering from cannabis dependence. Dual diagnosis is associated with poorer prognosis and more treatment resistance, cannabis dependence in particular is associated with higher risk for SCZ and more severe symptomatology. The group proposed that subjects with comorbid cannabis dependence and SCZ will display opposite alterations in DA transmission where the VST is blunted, as observed in alcoholics, while the preDCA is increased, as observed in schizophrenics. This dual dysregulation would explain the drive to use drugs (low DA in VST) leading to new or worse psychotic symptoms (drugs may dysregulate DA in preDCA), and poor compliance. Antipsychotics, aiming at treating psychosis, may exacerbate the hypodopaminergic tone in the VST leading to more craving, more drug use, non-adherence and a self-perpetuating vicious circle. Researchers in the Division are currently testing this model with [11C]raclopride and the amphetamine paradigm in non treatment seeking cannabis dependent subjects, matched healthy controls and dual diagnosis patients. Groups will be matched for age, gender, ethnicity, socioeconomic background, drinking habits and smoking habits.

**Biomarkers:** [18F]Fdopa studies in prodromal patients in collaboration with the COPE clinic aim at predicting conversion using [18F]fdopa uptake in the striatum as an indicator of who will convert to schizophrenia. This would guide treatment interventions

in this population, which in turn will minimize conversion rates or delay onset of the illness.

**Drug development:** A D1 agonist clinical trial funded by NIMH (PI: J. Lieberman) will start this coming year. IND pending. This will provide a proof of concept for cognitive enhancement in schizophrenia with subacute administration of a D1 agonist. PET occupancy will be measured in humans and in non human primates.

Imaging gene effects on receptors in the brain: this is an ongoing effort, with collection of DNA on all subjects who undergo imaging.

**MRS research:** In addition to the studies in schizophrenia, multiple collaborations with various investigators in the Institute are led by Dr Kegeles to measure GABA and glutamate in small voxels using state of the art techniques.

**Alcoholism Research:** The Division previously reported a regionally selective decrease in amphetamine induced DA release in the ventral striatum in recently detoxified alcohol dependent subjects compared to controls measured with high resolution Positron Emission Tomography (PET) and [11C]raclopride. D2 receptor density was decreased in all striatal substructures and was related to daily drinking prior to abstinence. Whether these alterations are a vulnerability factor to develop alcoholism, or a consequence of chronic alcohol exposure is unclear. The Division has now undertaken a series of studies aiming first at developing paradigms to assess dopamine release as sensitive probes for vulnerability, and at applying these paradigms in young at risk healthy volunteers to compare FHN and FHP subjects matched for drinking habits. These studies are funded by the Center for Translational Neuroscience of Alcoholism.

## Education and Training

The Division also trains fellows in the acquisition of the expertise and skills required for clinical investigation using PET, with focus on basic receptorology, neurochemistry, pharmacology and pharmacokinetics, in depth teaching of PET imaging, functional neuroanatomy, kinetic analysis on a region or voxel based approach, as well as general principles of clinical investigation (CGMP, statistics, drafting of IRB protocols).

Current fellows are:

Nina Urban, MD (2nd year)

Judy Thompson, PhD (third year)

Ramesh Neelamegam, PhD (1st year)

Ragy Girgis, MD (starts in 7/09)

## Grant Awards

## **NARSAD**

NARSAD Distinguished Investigator Award: Anissa Abi-Dargham, MD: Imaging dopamine release in prodromal schizophrenia.

## **Private Grants**

GSK contract (renewed for the third year): PI: Anissa Abi-Dargham, MD: Pharmacological evaluation of new compounds in non human primates.

AMGEN: PI: L. Kegeles: Pharmacological evaluation of new compounds in non human primates.

Intra Cellular Therapies Inc: PI: M. Slifstein: Pharmacological evaluation of new compounds in non human primates and rodents.

## **Awards and Honors**

Abi-Dargham: 6/08 to 6/09: President, Brain Imaging Council of Society for Nuclear Medicine

## **Highlights**

The Division of Translational Imaging continues to be the largest PET user in the Medical Center, accounting alone for more than 50% of research PET scans performed in the last year in the PET Kreitchman Center. In addition, MRS and fmri research, are more routinely performed to complement the information obtained with PET.

## **New Faculty**

Balu Easwaramoorthy, PhD, radiochemist.

## **Publications**

Slifstein M, Revisiting an old issue: the discrepancy between tissue ratio-derived binding parameters and kinetic modeling-derived parameters after a bolus of the serotonin transporter radioligand 123I-ADAM.. J Nucl Med. 2008 Feb;49(2):176-8. Invited Perspective

Martinez, D. G. Frankle. Slifstein, D.R. Hwang, J. Martin, M. Laruelle, A. Abi-Dargham, Imaging serotonergic transmission in recently detoxified alcoholics and healthy controls using [11C]WAY-100635 and [11C]DASB, Epub, Oct, 2008, Biol Psychiatry.

M Slifstein, B Kolachana, E H. Simpson, P Tabares, B Cheng, M Duvall, G Frankle, D R. Weinberger, M Laruelle and A Abi-Dargham: COMT genotype predicts cortical-limbic D1 receptor availability measured with [11C] NNC112 and PET, *Molecular Psychiatry*, 2008, 13(8):821-7.

Lawrence S. Kegeles, Mark Slifstein, W. Gordon Frankle, Xiaoyan Xu, Elizabeth Hackett, Sung-A Bae, Robyn Gonzales, Jong-Hoon Kim, Beatriz Alvarez, Roberto Gil, Marc Laruelle, Anissa Abi-Dargham: Occupancy of striatal and extrastriatal D2 by aripiprazole, an [18F]fallypride study: 2008, *Neuropsychopharmacology*, Dec;33(13):3111-25

Anissa Abi-Dargham, Elsmarieke van de Giessen, Mark Slifstein, Lawrence S. Kegeles, Marc Laruelle, Baseline and amphetamine stimulated dopamine activity are related in drug-naïve schizophrenic subjects, In Press, *Biol Psych*.