

## **The Lieber Center for Schizophrenia Research and Treatment**

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### **Overview**

Since its inception in 1999, the directive of The Lieber Center for Schizophrenia Research and Treatment has been to unite world-class researchers in finding the cause of schizophrenia and developing strategies for prevention and cure. It has been effectively mandated that the efforts of researchers be synergistic and maintain a translational level of analysis. Thus, the resources provided by The Lieber Center have fostered elemental breakthroughs and novel interactions among Columbia University's established and emerging basic, clinical, and pathophysiological researchers, and promoted successful collaborations with Yale University, University of Washington in Seattle, The Nathan Kline Institute, and The Kaiser Research Foundation.

The year 2006 has been a watershed research year. Phase I of The Lieber Center's five-year funding program drew to a close with a critical mass of innovative collaboration and patient oriented research (POR) synergism bringing into focus the results of the pilot-study research of the early years. Correspondingly, translational bridges from basic and clinical research findings to novel preventative and therapeutic strategies for psychosis, cognitive impairments, and emotional and social deficits in schizophrenia powered the genetic and neuroscience impact of experimental therapeutics in The Lieber Center's Phase II draft proposal.

### **Current Research**

*The Lieber Clinic for Comprehensive Care*

*Drs. David Kahn and Frederic Kass*

This program constitutes a bold and innovative initiative in the treatment of people with schizophrenia and represents a long-term commitment to patients and families who have lifetime needs that are

currently not being met. The Lieber Clinic for Comprehensive Care promises to be a unique resource for people with schizophrenia and their families. We look forward to building this exciting clinic, and with it, transforming the way in which schizophrenia is treated, ultimately, not only in New York but around the country and the world.

The Clinic is designed to combine psychiatric, medical and rehabilitation services under one programmatic umbrella. It will consist of an integrated, consumer-directed, individually tailored program that will offer comprehensive assessment, treatment and clinical management to patients with schizophrenia and related psychotic disorders. Although the program will provide services to the entire spectrum of patients with these illnesses, it will particularly focus on the chronically and severely ill individuals and their families for whom existing standard care is so often inadequate.

The program is staffed by clinicians who are experienced with this patient population and skilled in diagnostic assessment, motivational interviewing, intensive psychopharmacological management, neurocognitive remediation, social and vocational rehabilitation, psycho-education for patient and family, cognitive behavior therapy, dialectical behavior therapy, family therapy, peer support initiatives, case management/outreach and residential supervision. We focus on the whole patient and concern ourselves with both their mental and physical well-being. In this context, the Clinic staff collaborates closely with selected medical colleagues. The program is designed to maximize the patient's potential for independent living with optimal quality of life.

The Lieber Clinic Comprehensive Care will be an enduring conduit for the translation of the most current research that can be applied to the treatment of patients with schizophrenia. The goal of the Lieber Clinic is twofold; 1) to provide a comprehensive array of all clinical services that relevant to providing optimal care for a person with schizophrenia within a single clinical setting; and 2) circumventing the lengthy delays that are associated with the incorporation of new research findings into clinical practice by translating promising pharmacologic and somatic treatments into clinical care as soon as research has demonstrated that they are likely to be effective. This clinical component of the Lieber Center for Schizophrenia Research will provide leading-edge care for patients who have specific clinical needs, which remain unmet by existing FDA-approved medications, applying the very latest methods for which we have sufficient evidence. It will combine these medical advances with a full complement of therapeutic approaches, including an array of psychotherapeutic options and social, vocational, and support services.

*Center for Prevention and Evaluation (COPE)*  
Drs. Cheryl Corcoran and David Kimhy

COPE is a "prodromal" research program created specifically for adolescents and young adults (age 12-25) identified as at heightened risk for psychosis, as compared with their peers, on the basis of attenuated symptoms, functional impairment and/or family history. COPE was established in 2003 and has since enrolled nearly 40 young people in its ongoing 2-year study protocol. The COPE clinic has a staff of 13 and provides a full range of clinical care free of charge (excluding prescribed medication) to young people in the program and clinical supervision to psychiatry medical residents, and psychology and social work interns. Drs. David Printz and R. Anna Seckinger oversee clinical care, Dr. David Kimhy is the deputy director of research, and Dr. Shamir Khan and Julie Walsh, MA, are project managers.

Research at COPE involves the evaluation of trajectories of symptom development and neural changes, biomarkers for psychosis risk, and proximal exposures such as stress and drug use. Since its induction into The Lieber Center in 2006, several young investigators have initiated research projects at COPE and senior collaborative research with Lieber Center investigators includes: 1) multimodal longitudinal imaging (Drs. Tiziano Colibazzi and Bradley Peterson), 2) brain perfusion (Drs. Scott Schobel and Scott Small), 3) spectroscopy (Dr. Lawrence Kegeles), 4) striatal dopamine synthesis (Dr. Anissa Abi-Dargham) and, 5) event related potentials (Dr. Gerard Bruder). In addition, the pervasive social dysfunction of schizophrenia and its prodrome is being studied through translational studies with the Lieber Center Animal Models Core.

Future research directions for COPE include treatment trials with both CBT and novel pharmacologic strategies, and the provision of clinical and research training to visiting fellows (i.e., Koplewitz fellows) from other countries (currently, Singapore, Spain and Israel) who intend to launch and develop prodromal research programs in their home countries.

#### *Genetic Models of Schizophrenia in the Mouse*

Drs. Eric Kandel, Christoph Kellendonk, Eleanor Simpson and H. Jonathan Polan

The Kandel lab has been focusing on the cognitive symptoms of schizophrenia and particularly on prefrontal cortex and working memory. They had shown earlier that excess dopamine D2 receptor expression in the striatum comparable to that which is found in schizophrenic patients leads to cognitive deficits that are restricted to prefrontal cortical function. This deficit persists when the gene is turned off, indicating that the prefrontal cortical dysfunction typical of schizophrenia may be a late manifestation of D2 receptor over-expression in early development. The Kandel laboratory went on to show that these changes are due to alterations in D1 activation in the prefrontal cortex. In the last year they have been using this mouse genetic model to examine the “double hit” hypothesis: that most cases of schizophrenia are due to the combined actions of genetic susceptibilities with an environmental insult. Prenatal restraint stress was used on pregnant dams carrying D2 transgenic offspring during the third trimester. The offspring of these dams were behaviorally tested as adults for evidence that the transgene interacts with the prenatal stress to produce new symptoms not produced by the transgene or the stress alone. The results demonstrated such an interaction: a new dimension of deficit emerged in the social behavior test, an index of the negative type of schizophrenia-like symptoms. The Kandel lab continues to look for other negative symptoms related behaviors in this double hit paradigm, and we are investigating the molecular mechanisms of this phenomenon.

A number of single nucleotide polymorphisms (SNPs) in the gene encoding Catechol-O-methyltransferase (COMT) have been associated with schizophrenia. One specific SNP in the COMT gene, the Val158Met polymorphism, codes for either valine or methionine at amino acid position 158 in the polypeptide sequence. The valine form, which is more active than the methionine form, results in faster breakdown of dopamine and thus decreases dopamine’s availability at PFC synapses. This specific allele has been associated with schizophrenia in family studies and with poor performance on prefrontal mediated cognitive skills in patients with schizophrenia, their unaffected relatives, and control individuals. To understand how COMT hyperfunction may lead to deficits in cognitive function, the Kandel lab have generated transgenic mice that over-express COMT in the forebrain under a temporally

controllable promoter. The temporal control permits separation of the consequences of COMT over-expression during development and during adulthood. So far a number of transgenic lines have been generated and have been examined for their expression patterns. One line which expresses strongly in the whole forebrain has been examined for protein levels and it has been determined that the increased mRNA level results increased expression of the protein. We are now in the process of analyzing the physiological and behavioral phenotype of this exciting new animal model.

#### *Clinical Neurobiology*

Dr. Dolores Malaspina and Deborah Goetz

The Division of Clinical Neurobiology conducts research in both epidemiological samples and clinical populations to study how genetic susceptibility, environmental exposures and their interactions can influence the risk for psychotic disorders. The clinical research studies include individuals at risk for psychosis and those with schizophrenia and bipolar disorder. These studies focus on prevention, targeted treatments, and curtailing deterioration and aim to improve the lives of individuals with severe mental disorders.

The training of schizophrenia researchers and expert clinicians is an important activity for this department. The division supports the training activities of four funded and two pending NIMH career development awards, and two post doctoral fellows. A number of scientists also train in epidemiology, clinical investigations and translational research projects.

#### *Clinical Core*

Drs. Abi-Dargham, Roberto Gil, Lawrence Kegeles, Zafar Sharif, and Paul Rosenfield

The Clinical Therapeutics program of the Lieber Center is a multifaceted program aiming at serving patients' needs while providing a clinical basis for testing new concepts emerging from the translational studies performed in the other sections of the Center. This is a highly interactive integrative program based on frequent communications within the group of Lieber investigators and with the outside scientific community at large.

Over the last few years we successfully established an outpatient Lieber research Clinic that complements and extends the missions of the Schizophrenia Research Unit. This is a state of the art program where caring clinical care coexists with the latest imaging investigations and proof of concept research studies as well as the most promising Clinical Trials.

Our imaging studies continue in search of the cellular and molecular significance of the disturbances we previously identified in schizophrenia, using new tracers to image extrastriatal dopamine and tracers to test the affinity states of the dopaminergic receptors. In addition to the imaging studies aiming at understanding the pathophysiology of the illness, other will focus on using imaging to develop biomarkers for prevention or therapeutic targeting strategies. These include [18F]fDOPA studies in prodromals and imaging D1 in combination with treatment by a D1 agonist.

We have expanded our arsenal of treatment studies, as we represent one of the sites of the TURNS initiative. We offer the latest therapeutic interventions, selected by an expert group as the most promising approaches to the treatment of schizophrenia. These include studies with N-

desmethylclozapine and ampakines. Studies using a D1 agonist and muscarinic M1 agonists are planned to start soon.

Our clinical program also includes genetic testing to build a database of samples that can be used to investigate biological associations of new genes found in schizophrenia to the relevant molecular targets in the brain or to the response to a particular therapeutic intervention. Dr. Gerard Bruder and his colleagues found that catechol-O-methyltransferase (COMT), a candidate gene for schizophrenia, was associated with performance on working memory tests that require higher-order mental manipulation, but not on tests that measure simple storage of information.

In summary, we have a multidimensional multidisciplinary approach to unraveling the mysteries of schizophrenia and developing better treatments for the future.

#### *Neurobiological Bases of Molecular Imaging*

Dr. Jonathan Javitch

We have continued to examine the mechanism of amphetamine-induced dopamine efflux by the dopamine transporter (DAT) and the potential involvement of DAT in mediating the enhanced amphetamine-induced inhibition of raclopride in imaging studies of patients with schizophrenia. In collaboration with our colleagues we have shown that the kinase CaMKII physically interacts with the C-terminus of DAT and phosphorylates the N-terminus to increase dopamine efflux. We have further demonstrated that amphetamine activates CaMKII. We have now succeeded in creating 2 novel lines of knock in mice. In the first, we have neutralized the serines in the N-terminus of DAT, thereby creating a mouse in which dopamine uptake should be normal but amphetamine-induced efflux should be impaired. Another line expresses a transporter that is constitutively pseudophosphorylated, which should allow amphetamine to induce release, but in an unregulated fashion. During the coming year we will begin to test these mice using neurochemical, electrophysiological, and behavioral paradigms to explore their acute and chronic responses to amphetamine.

#### *Treatment approaches based on the PCP/NMDA model*

Dr. Daniel Javitt

Research conducted at Nathan Kline Institute (NKI) continues to focus on new treatment approaches based upon the PCP/NMDA model. Phencyclidine (PCP, “angel dust”) induces symptoms closely resembling those of schizophrenia by blocking neurotransmission at N-methyl-D-aspartate (NMDA)-type glutamate receptors, suggesting that endogenous dysfunction or dysregulation of NMDA receptors may play a critical role in schizophrenia. Current investigations are aimed at identifying treatments that can augment NMDA neurotransmission in humans, while simultaneously improving models for new treatment development in animals.

Clinical activities being performed as part of the Lieber center include toxicity assessment of natural amino acid D-serine, and preparation for a multicenter US clinical trial. Efficacy of D-serine has recently been investigated in overseas trials in Taiwan and Israel with noted significant improvements in negative, positive and cognitive symptoms. Based upon these findings, NIMH has awarded NKI a Cooperative Drug Development Grant (CDDG) for a multicenter D-serine treatment study to be conducted in both chronic and prodromal individuals with schizophrenia. The project is scheduled to

begin as of 10/1/05, pending FDA acceptance of preclinical toxicity findings, and will be performed in collaboration with Lieber center funded recruitment/treatment centers for chronic and prodromal patients with schizophrenia.

On a preclinical level, studies have been investigating potential etiological mechanisms of NMDA dysfunction in schizophrenia, as well as development of new models for drug development. One of the best-established recent findings in schizophrenia is a disturbance in brain structure as detected using Diffusion Tensor Imaging (DTI). DTI scanning provides a measure of brain white matter integrity. In schizophrenia, white matter measures are reduced in both sensory and cognitive regions. Lieber-associated projects at NKI have recently demonstrated that DTI signals can be detected even in preserved postmortem brains. Current studies are evaluating the degree to which NMDA dysfunction may cause DTI changes similar to those observed in schizophrenia, as well as the degree to which deficits may be reversed by NMDA agonists such as d-serine.

#### *Animal Models Neurobehavioral Analysis Support Core*

Dr. Holly Moore

Since 2003, many investigators of the Lieber Center, including Lorna Role, David Talmage, Stephen Rayport, Jay Gingrich, Eric Kandel, Anissa Abi-Dargham and Holly Moore have used common facilities to conduct behavioral and limited systems neuroscience testing in rodent models relevant to schizophrenia. In the past two years, this cooperative has been progressively shaped into a core facility that allows investigators to design and execute a set of *in vivo* experiments that will test schizophrenia-relevant hypotheses in genetic and epigenetic rodent models as they are developed. This system allows investigators with innovative models to have access to the expertise and facilities they need to determine the relevance of their model to schizophrenia research.

The core is currently under development with the goal of providing expanded services to investigators. Schizophrenia is especially challenging to model in animals because it lacks a disease-specific neuropathology and because diagnosis is based on psychopathology, with few if any behavioral homologues in experimental animals. Thus, the state of research in schizophrenia is not such that we can use genetic, neuropathological or behavioral models as “standard” systems for discovering therapeutic targets or screening potential therapies. For this reason, a rodent modeling core must be designed as 1) a multi-level resource for the development and validation of models, specifically testing homology between a model and reliable neural-behavioral phenotypes in schizophrenia, 2) a repository of tools (behavioral pharmacological assays and models of pathophysiology) for determining contributions of patient exposures (primarily drugs) to biomarkers, and 3) a site for “smart-throughput” testing of potential therapies, i.e., using the optimal animal model system(s) for a given potential therapy.

#### **Grants**

Anissa Abi-dargham, PI, IMH P50 066171-030001: Prefrontal Dopamine Function in Schizophrenia

Anissa Abi-Dargham, PI, NIMH P50 066171-039003: Clinical Core

Anissa Abi-Dargham, PI, NIMH K02 064178-04: Prefrontal Cortical Dopamine and Cognition in Schizophrenia

Alan S. Brown, PI, NIMH K02 065422-04: Epidemiology of Prenatal Exposures in Schizophrenia

Alan S. Brown, PI, NIMH R01 073080-01A1: Prenatal Factors and Risk of Bipolar Disorder

Gerard Bruder, PI, NIMH R01 066597-03: Subtypes of Schizophrenia: ERPs During Memory Processing

Cheryl Corcoran, PI, NIMH K23 066279-03: Schizophrenia Risk to Onset: Neurobiology and Prevention

Jay Gingerich, PI, NIMH R21 073794-02: Epigenetic Mechanisms: Paternal Age and Neural Function

Eric Kandel, PI, NIMH P50 066171-030005: Mouse Models of DA and Glutamate Dysfunction

Eric Kandel, IP, NIMH R01 045923-16A1: The Role of Neuronal Integration in Working Memory

Lawrence Kegeles, PI, NIMH K08 001594-05: Dopamine and GABA Imaging in Schizophrenia,

Jeffrey Lieberman, PI, NIMH P50 066171-03: Neurobiology of Dopamine in Schizophrenia

Jeffrey Lieberman, PI, NIMH U01 076544-01: Pharmacologic and Clinical Testing of a D1 Agonist for Neuropsychiatric Disorders

Holly Moore, PI, NIMH P50 066171-039001: Core-Neurochemistry

Lorna Role, PI, NINS R01 029071-16: Expression of Neuronal Nicotinic Acetylcholine Receptors

Lorna Role, PI, NIDA R21 019941-02: In Vivo Studies of Neuregulin 1 in Addiction Pathways

Arielle Stanford, PI, K23, Transcranial Magnetic Stimulation and Negative Symptoms in Schizophrenia

### **Awards/ Honors**

Cheryl Corcoran, Florence Irving Assistant Professor of Psychiatry

Cheryl Corcoran and Dolores Malaspina, APIRE/Kempf Fund: APA Kempf Fund Award for Research Development in Psychobiological Psychiatry, Cheryl Corcoran

Alex Dranovsky, NARSAD Young Investigator Award: Effects of stress and antidepressants on cellular and circuit plasticity of adult-born hippocampal neurons, Alex Dranovsky

Jonathan Javitch, Chair, The Gordon Research Conference, Membrane Transport Proteins in Health and Disease, Biddeford, Maine.

Lawrence Kegeles, Dana Foundation Award: Dana Program in Brain and Immuno-Imaging, Mapping abnormal excitatory and inhibitory neurochemical circuitry in schizophrenia with R TMS and MRS

Jeffrey Lieberman, Eugene A. Hargrove Mental Health Research Award, North Carolina Foundation for Mental Health Research, Inc., North Carolina Psychiatric Association, NCPA

Jeffrey Lieberman, NARSAD, Lieber Prize for Schizophrenia Research

Scott Schobel, Collegium Internationale Psychopharmacologium (CINP) Young Investigator

Scott Schobel, The Pisetsky Award for Schizophrenia Research

Arielle Stanford, NARSAD Brian Bass Young Investigator Award: A new tool on the road to restoring function: repetitive transcranial magnetic stimulation for the negative symptoms of schizophrenia

Arielle Stanford, Paul Janssen Translational Neuroscience Fellow

## Highlights

In 2006 the Lieber Center moved to include the Center of Prevention and Evaluation (COPE) which, in conjunction with the Department of Medical Genetics, identifies and treats young prodromal subjects with the aim of developing diagnostic at-risk criteria for clinical use and pre-first-episode preventative programs.

***Lieber Clinic for Comprehensive Care*** has been established as a new program dedicated entirely to the rapid, effective translation of the most recent valid data on prevention and therapeutics. This new clinical program will utilize the latest advances made by the Lieber group, and by other public and private investigators from around the world, to offer new therapies and optimize existing therapies. Advances in identification of biomarkers will be used to refine diagnosis of individuals, and optimize their individualized pharmaco- and behavioral therapy.

## Publications

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### Chapters

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