

**Division of Molecular Imaging & Neuropathology (formerly Neuroscience)
2006-2007**

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2. Overview

The Division of Neuroscience spans the research spectrum from basic cell biology to *in vivo* imaging, molecular genetics and treatment trials. It emphasizes translational research and employs a multidisciplinary approach to psychiatric research to examine the biological substrate of mental illness at multiple levels. The Division comprises laboratories and research groups that range from basic molecular signal transduction and laboratory model studies to treatment studies. More specific research areas include neuroanatomical mapping; quantitative morphometric and gene expression studies in human, nonhuman primate and rodent brains; postmortem brain studies of psychiatric disorders; and providing neuropathology services to the New York State Office of Mental Hygiene (OMH). The Division maintains an archival collection (brain bank) of these

specimens as well as other brain specimens collected for research purposes. The *Brain Imaging group* conducts functional and structural brain imaging studies in rodents, baboons and human subjects. This subdivision develops novel PET ligands for monoamine receptors, enzymes and transporters, amyloid protein and peptide receptors. It studies disease processes, effects of gene variants and childhood adversity on brain biology, biologic predictors of treatment outcome and the use of biomarkers for studies of drug effect and the relationship of drug actions to occupancy of the hypothesized site of action.

The Division of Molecular Imaging & Neuropathology (formerly Neuroscience) is one of the largest at NYSPI and conducts a range of basic and clinical studies. It has three center grants. The NIMH-funded Silvio O. Conte Center for the Neuroscience of Mental Disorders: The Neurobiology of Suicidal Behavior investigates risk factors for suicidal behavior in mood disorders, schizophrenia, and personality disorders with PI John Mann. The Conte Center utilizes human postmortem studies and translational approaches, such as novel PET tracers for brain imaging, new peptide assays in cerebrospinal fluid, and an investigation of candidate genes and basic biologic and cognitive endophenotypes. The second center is the Moody Center for the Study of Early Onset Bipolar Disorder, headed by Maria Oquendo. This center seeks to use functional MR and genetics to detect early onset bipolar disorder as a step towards preventative intervention. The third center is the NIMH-funded Developing Center for Interventions in the Prevention of Suicide, headed by Barbara Stanley.

3. Current Research

The major areas of clinical investigation have been the biological basis of mood, anxiety and psychotic disorders, the action of antidepressants and other psychotropics, and risk factors for suicidal behavior. Basic studies have involved studies of neurotransmitter systems and the action of antipsychotics and antidepressants.

The NIMH-funded Silvio O. Conte Center for the Neuroscience of Mental Disorders (MH062185; PI: John Mann) supports studies into the risk factors for suicidal behavior in mood disorders, schizophrenia, and personality disorders. This work has defined a more comprehensive model of suicidal behavior based on clinical and biological findings from a large prospective study that utilizes novel PET tracers for brain imaging, new peptide assays in cerebrospinal fluid, candidate gene profiling and more basic endophenotypes of stress responsiveness.

Mood Disorders & Suicide Risk Clinical Research: Dr. Maria Oquendo coordinates the clinical/biological studies in the Division. Drs. Michael Grunebaum, Gregory Sullivan, Leo Sher and Elizabeth Sublette conduct psychobiological studies of mood and psychotic disorders. Dr. Peter Freed studies mood regulation and grief process using fMR. Dr. Ainsley Burke trains and supervises the clinical evaluation core research staff and works on aspects of familial transmission of adversity. The studies of suicidal behavior in schizophrenia are directed by Dr. Jill Harkavy Friedman. Neuropsychological studies of cognitive function and impulsiveness in mood, psychotic and personality disorders are conducted by Dr. John Keilp. Dr. Barbara Stanley conducts neurochemical and psychological investigations in borderline personality disorder. One of her NIMH grants supports a parallel group, randomized, double blind study of the efficacy of a psychotherapy called dialectical behavior therapy versus an SSRI medication in the

prevention of suicidal behavior in borderline personality disorder. Dr. Oquendo has an NIMH grant to conduct a double blind, randomized treatment study comparing lithium and divalproex maintenance treatment on suicidal behavior in bipolar disorder. Drs. Stanley and Oquendo head a Developing Center for Interventions to prevent suicide funded by NIAAA. Drs. John Mann, Maria Oquendo, and Ramin Parsey have developed methods using Positron Emission Tomography (PET) for quantifying binding to serotonin receptors. These techniques allow study of mood disorders, the effect of treatment with medication or ECT, and identification of high-risk patients, prediction of clinical response to antidepressants and the localization of regional brain abnormalities in high-risk patients. These studies identify specific prefrontal cortical regions that determine lethality of suicidal behavior by mediating the degree of intent and impulsivity, which, in turn, determine the medical lethality of suicidal behavior. They have also mapped the brain regions with abnormal serotonin system function in depressed patients and identified regions of abnormality associated with specific components of psychopathology. The Family Center conducts studies of bipolar probands and their offspring and is headed by Dr. Maria Oquendo. Other studies examine genetic influences on the manifestation of suicidal and self-harming behaviors in collaboration with Drs. Joe Terwilliger, Victoria Haghighi and Jim Russo, of the Columbia Genome Center, Dr. René Hen of the Center for Neurobiology and Behavior, and Dr. David Brent of the University of Pittsburgh. Several key genes have been found to be associated with mood disorders, or substance abuse or aggressive/impulsive traits and others with suicidal behavior. A study of the familial transmission of depression, suicidal acts and impulsive-aggressive traits is funded by NIMH grants to Dr. Mann and Dr. Brent (in Pittsburgh).

Neuropharmacology: Dr. Hadassah Tamir and her associate, Kuo-peing Liu continued the study of transduction pathways downstream of 5-HT_{1A} receptor. Their study strongly suggest that activation of this serotonergic receptor is crucial for cell survival. Blockade of the receptor increases pro-apoptotic agents levels and attenuates the production of anti-apoptotic molecules. Abnormal serotonergic transmission, suggested to be a major cause of depression, may affect not only the synaptic transmission induced by various serotonergic receptors, but also the health of the cells that are activated by 5-HT_{1A} receptor. The work is carried out at two levels. They study the transduction pathways downstream of 5-HT_{1A} receptors expressed on cell line. This provides them with information about the molecules that participate in the pathways and their interrelation. Knowledge obtained from the cellular study is then applied to study postmortem brain tissue obtained from depressed suicide victims and their matched controls. Aberrations in the pathways, as expressed in brain of suicide victims, may shed light on the pathology of depression/suicide.

Serotonin Neurophysiology and MicroPET: Dr. Mark Underwood conducts research into the regulation of serotonergic neurons in the dorsal raphe nucleus in the postmortem human brainstem in suicide and alcoholism. The studies examine serotonergic neurons directly and define their functional capacity using quantitative morphometric and receptor binding methods. Dr. Underwood and colleagues are also performing translational studies examining gene-environment interactions and effects on the development of the serotonergic system in the brain of transgenic mice and how this affects behaviors in adulthood. He directs the Department of Neuroscience *in vivo* imaging studies in rodents using microPET methods supported by the Radioligand Laboratory of Columbia University. He chairs the Columbia University Medical Center Institutional Animal Care and Use Committee (IACUC).

Human Genetics and Neurochemistry: Dr. Mann and Yung-yu Huang have been studying CSF monoamine metabolites and other neurotransmitter systems including peptides such as CRF and substance P, GABA and glutamate in human in collaboration with Tom Cooper. Studies of genetic and rearing effects on neurotransmitter levels in CSF and on the behavior in non-human primates are also conducted in collaboration with Drs. Jay Kaplan, Jeffrey Rogers, Cliff Jolly and Lynn Fairbanks. With Drs. Haghghi, Terwilliger, Gilliam, Russo and Goldman, candidate genes such as 5-HTR_{1A}, 5-HTR_{1B}, 5-HTR_{2A}, HTT and TPH₁ and TPH₂ are being studied in postmortem brain tissue and blood or saliva samples from families and unrelated patients and controls to examine genetic and environmental effects on the brain and psychopathology with conventional and advanced DNA microarray techniques. Dr. Haghghi has two NIH grants to study genome-wide methylation patterns in mood disorders and mapping these effects onto candidate gene loci identified by SNP and expression arrays.

Neuropathology

The Division of Neuropathology conducts basic and clinical research and participates in postgraduate medical education. It provides a neuropathology service to the New York State Office of Mental Hygiene (OMH). The Neuropathology Division examines the brains of OMH patients obtained at autopsy and it maintains an archival collection of these specimens.

Chemical Neuroanatomy and The Diane Goldberg Laboratory for Molecular Imaging of Neural Disorders: Dr. Victoria Arango and her colleagues conduct postmortem studies of suicide victims and alcoholics that utilize a combination of quantitative receptor autoradiography, *in situ* hybridization histochemistry and morphometric analysis of forebrain and brainstem nuclei. Her collaborators are Drs. Mark Underwood, Hadassah Tamir, J. John Mann, Helene Bach-Mizrachi, Loubna Erraji-Benchekroun and Maura Boldrini, as well as Suham A. Kassir and Yung-yu Huang. Drs. Arango, Dwork and Rosoklija direct the Brain Bank of the Conte Center for the Neuroscience of Mental Disorders. All cases, now collected in the Republic of Macedonia, undergo a detailed psychological autopsy, a toxicological screen including brain and hair analyses and neuropathological examination. In addition to demonstrating that suicide victims do not have fewer serotonin-synthesizing neurons or processes in the dorsal raphe nucleus, Dr. Arango and colleagues showed an increase in the level of tryptophan hydroxylase (TPH) protein and mRNA in the brainstem of suicide victims.

Using 3-D stereology, they found decreased neuronal density in the orbital, but not in the dorsal prefrontal cortex of suicide victims. They derived a *binding index*, the ratio of receptor binding to neuron density (fmol/mg tissue)/(neurons/mm³). 5-HT_{1A} and 5-HT_{2A} binding indices were higher in orbital cortex in the suicide group, but were not different in BA9. These results lend support to a serotonergic abnormality in the ventrolateral prefrontal cortex of the brains of suicide victims, while the dorsolateral prefrontal cortex is largely spared.

Taken together, these studies revealed fundamental neurochemical differences between suicide victims and mood disorder patients. They indicate that morphological differences between controls and suicides are primarily confined to the ventral prefrontal cortex, while the dorsal prefrontal cortex remains largely unaffected. A collaboration with Dr. Lisanby, examines the neuroanatomical effects of electroconvulsive therapy and

magnetic seizure therapy in nonhuman primates, including the examination of cell proliferation in the hippocampal formation following these seizure-inducing interventions. Other collaborations of Dr. Arango include postmortem studies of the cannabinoid 1 receptor with Dr. Vinod Yaragudri and Appa Hungund from the Nathan Kline Institute and molecular biology studies with Charles Glatt from Weill-Cornell. Dr. Arango also collaborates with Dr. Fatema Haghighi on a methylation study in depression and with Dr. Gil Zalsman on a SNP study of depression and suicide. These various projects are supported by NIMH, NIAAA, The Stanley Medical Research Institute, and the American Foundation for Suicide Prevention for postmortem human brain research. A postdoctoral research fellow, Dr. Boldrini, as well as the Junior faculty, Dr. Scalia, Dr. Bach-Mizrachi and Dr. Erraji-benchekroun, have all secured AFSP and NARSAD awards. Dr. Boldrini is the recipient of the Janssen Fellowship for Translational Neuroscience.

Neuropathology: Dr. Andrew J. Dwork and colleagues study neuropathological features of schizophrenia and mood disorders, and neuropathological correlates of the dementia that is common among elderly individuals with schizophrenia. Current projects include: (1) Structural abnormalities of dendrites in schizophrenia, mood disorders, and animal models of these illnesses and their treatments. These studies employ our NeoGolgi method of neuronal impregnation, which is the first to provide predictable and uniform Golgi impregnations. Animal studies are conducted in collaboration with Drs. Coplan, Gingrich, Lisanby, Moore, Perera, and Role. (2) Neuropathological correlates of dementia in schizophrenia. These studies are currently focused on white matter pathology. (3) Collection of brains and clinical data from autopsies of psychiatric patients, suicides, and comparison cases in the Republic of Macedonia. Material from this collection is employed in numerous studies within the Department of Neuroscience and in collaboration with other departments and institutions. (4) A historical study using the ecological introduction of neuroleptic drugs to determine the effect of the duration of untreated psychosis on the course of schizophrenia after the initiation of antipsychotic treatment. (This is a NARSAD Young Investigator project by Dr. Branislav Mancevski.) (4) Studies of the role of neurogenesis in the response of animal models of depression to antidepressant treatments. (5) A multi-laboratory collaboration, organized by Dr. Alan Brown, to investigate abnormalities of microtubules in schizophrenia and animal models of schizophrenia. Three new grants were awarded during this period to Dr. Dwork: the Stanley Medical Research Institute Neuropathology of White Matter in Schizophrenia #07R-1809; the American Foundation for Suicide Prevention White Matter Integrity and Suicide Risk: Histologic Evaluation of Potential DTI Targets and the NIMH Myelin Pathology in Schizophrenia Grant (R01 MH060877-09).

Brain Imaging

Ramin V. Parsey MD, PhD is the Director of the Brain Imaging Core. Dr. Todd Ogden is the senior brain image analysis statistician and has developed novel innovations in methods and software for kinetic modeling and analysis of PET neuroreceptor binding studies. Dr. Ogden, together with the kinetic modeling expertise of Dr. Ramin Parsey, and the programming skills of Dr. Ashish Ojha, has developed a new voxel-based image analysis routine.

Highlights: For the first time the laboratory developed a novel agonist radiotracer for use in humans to image high affinity serotonin 1A receptors, [¹¹C]CUMI-101. To our knowledge, this is the first positron emission tomography tracer developed from scratch

to go into human use at the institution.

Current Research in the Brain Imaging Division: The Division is continuing to study major depression and bipolar depressed subjects before and after treatment with an SSRI or ECT, suicide attempters and non-attempters, anxiety disorders and healthy volunteers. These studies have generated important new data that for the first time demonstrate that many of our findings in postmortem human brain tissue can be detected in vivo in depressed subjects. Abnormalities detected in currently depressed subjects are now being investigated in remitted depressed subjects in an effort to determine if biological abnormalities are state or trait phenomena.

Drs. Dileep Kumar, Jaya Prabhakaran and Vattoly Majo are an outstanding group of organic chemists. As a result of their expertise, as stated in the highlights, we report the first in human PET agonist radiotracer for the 5-HT_{1A} system, CUMI-101.

Dr. Jeffery Miller received a NARSAD Young Investigator Award for work using functional MRI to predict treatment response in major depressive disorder.

Dr. Elizabeth Sublette, recently appointed as an Assistant Professor in the Columbia University Department of Psychiatry, is the recipient of two foundation awards, a Pilot Award from the American Foundation for Suicide Prevention, and a NARSAD Young Investigator Award, for studies concerning the influence of dietary fatty acids on brain functioning.

Dr. Peter Freed received funding to study grief process with fMRI.

We collaborate on NIH funded imaging studies with Dr. Davangere Devanand in Biological Psychiatry, Dr. Evelyn Attia in Eating Disorders, Dr. Richard Sloan in Consultation Liaison Psychiatry, Paul Harris and Rudi Liebel in Diabetes, Yaacov Stern in Neurology. We have funded studies from several companies for occupancy studies with new therapeutic agents and for development of novel PET tracers for new molecular targets. Ongoing funding from NIMH and foundations include two center grants (Conte Center for the Neuroscience of Mental Disorders and The Stanley Medical Research Institute), NIMH R01 grants, a NIH K01 award, NIMH K08 grants, American Foundation for Suicide Prevention grants, Clinical Trials Office, Dana Foundation and NARSAD grants.

4. Awards/Honors

Dr. Andrew Dwork was permanently appointed as Visiting Professor of Pathology, University "Ss. Cyril Methodius," Skopje, Macedonia

Dr. Maria A. Oquendo was named Director of Ambulatory Research Clinics in 2006.

Dr. Oquendo was named Vice Chair for Education in 2007.

Dr. Elizabeth Sublette received an award from the American Foundation for Suicide Prevention, Pilot Award. "Pilot Study of Effects of Essential Dietary Polyunsaturated Fatty Acids on Brain Metabolism in Depression and Suicide." In 2006

Dr. Sublette received a 2007 NARSAD Young Investigator Award, “Assessing the Relationships Between Plasma Fatty Acid Levels and Brain Serotonergic Functioning in Major Depressive Disorder and Suicide Risk.”

Dr. Victoria Arango continues as President of the Alumni Association School of Graduate Studies, SUNY Downstate Medical Center, a post she has held since 2004.

Dr. Arango received a five year competitive continuation of MH-40210-22 Postmortem neurochemical Studies of Suicide from 5/1/2007 to 4/30/2012

In 2006 Dr. Arango received a Distinguished Investigator Award from the American Foundation for Suicide Prevention “*Studies of Corticotropin Releasing Hormone in the Amygdala of Suicide Victims*”

In 2006 Dr. Underwood received a Distinguished Investigator Award from the American Foundation for Suicide Prevention “*Serotonergic and Noradrenergic Imbalance in Bipolar Suicide*”

Dr. Arango delivered the Keynote Address “*The Neurobiology of Suicide with Emphasis in the Serotonergic System*” at the XXI Annual Research Meeting of the National Institute of Psychiatry, Mexico City, Mexico, October 4, 2006

In 2006, Dr. Mann became the Vice Chair and Director of Research for the Department of Psychiatry, Columbia University and the New York State Psychiatric Institute

In 2007, Dr. Arango became a Member of the CoAP Committee, New York State Psychiatric Institute

In 2007, Dr. Arango became a Member of the Research Grants Committee, American Foundation for Suicide Prevention

In 2007, Dr. Arango became a member of the Program Committee, Society for Biological Psychiatry

In 2007, Dr. Arango was appointed for a second term at the Credential Committee, American College of Neuropsychopharmacology

Mark Underwood, Ph.D. was promoted to Professor of Clinical Neuroscience in Psychiatry

Dr. Underwood received a Distinguished Investigator Award from the American Foundation for Suicide Prevention

5. Publications 06-07

Arango V, Mann JJ. Abnormalities of Brain Structure and Function in Mood Disorders. In: *Neurobiology of Mental Illness*, 3rd Edition. Charney DS and Nestler EJ (eds). Oxford University Press, New York. In Press.

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