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FOR IMMEDIATE RELEASE

Brain & Behavior Research Foundation Awards NARSAD Distinguished Investigator Grants Valued At $1.5 Million to Scientists Pursuing Innovative Mental Health Research

NEW YORK CITY (December 8, 2016)—The Brain & Behavior Research Foundation today announced the award of NARSAD Distinguished Investigator Grants valued at $1.5 million to 15 scientists, who are full professors or the equivalent, conducting innovative projects in diverse areas of neurobiological and behavioral research. Recipients of the $100,000 one-year grants seek new potential targets for understanding and treating psychiatric disorders that affect one in five people, including bipolar disorder, depression, multiple types of mental illness, schizophrenia, and post-traumatic stress disorder.

Recipients of the 2016 NARSAD Distinguished Investigator Grants were selected by the Foundation's Scientific Council, which is composed of 173 leading experts across disciplines in brain and behavior research, including two Nobel laureates; four former Directors of The National Institute of Mental Health and the current Director; four recipients of the National Medal of Science; 13 members of the National Academy of Sciences; 26 chairs of Psychiatry and Neuroscience Departments at leading medical institutions; and 55 members of the National Academy of Medicine.

"The Distinguished Investigator awards provide support to encourage established scientists to advance our understanding about mental illness, and brain and behavior disorders," says Foundation President and CEO **Jeffrey Borenstein**, **M.D.** "These grants fund creative research to explore new ways of preventing, diagnosing and treating psychiatric disorders."

"The Brain & Behavior Research Foundation's NARSAD grants are remarkable because they serve as seed capital for new approaches that might otherwise go unfunded," said **Jack D. Barchas, M.D**, Chair and Barklie McKee Henry Professor of Psychiatry at Weill Cornell Medical College, and

Psychiatrist-in-Chief at Weill Cornell Medical College, NewYork-Presbyterian Hospital and Paine Whitney Clinic, who chairs the Scientific Council's Distinguished Investigator selection committee. "This year, we received a large number of outstanding proposals with the potential to inform several illnesses, reveal new neurobiological or behavioral targets for potential treatment, explore exciting new basic science, pursue translational scholarship and multidisciplinary collaborations, and conduct new early treatment trials that center on new approaches or ways to combine treatment."

The Recipients of the 2016 NARSAD Distinguished Investigator Grants are as follows:

Bipolar Disorder:

Roel A. Ophoff, Ph.D., of the *University of California, Los Angeles*, will explore how disruptions in circadian rhythms – our internal 24-hour clock – influence bipolar disorder. Dr. Ophoff has collected tissue samples from 100 patients with severe bipolar disorder as well as 100 samples from healthy individuals, and has generated cell cultures from these samples. Dr. Ophoff will use the cultures to examine the molecular regulatory mechanisms underlying the circadian clock. The goal is to use data-driven statistical tools to objectively identify genes and gene clusters that show clock-like patterns of expression. Dr. Ophoff hopes that this work will lay the foundation for systematic investigation of the involvement of the circadian clock in bipolar disorder.

Depression:

Jay M. Baraban, M.D., Ph.D., of the *Johns Hopkins University School of Medicine*, will explore the role of unconventional molecular pathways in depression. Much of our current knowledge and treatments for depression are focused on a few narrow pathways. Unfortunately, many patients do not respond to current therapies, suggesting that additional pathways may contribute to depression. Dr. Baraban will focus on a group of cellular signaling molecules known as microRNAs. In previous studies, reduced levels of microRNAs have been associated with depression-like behavior in mouse models of the illness. Dr. Baraban is working to understand how the machinery that is responsible for microRNAs degradation affects behavior. His goal is to find inhibitors for this pathway that may serve as novel alternative treatments for depression.

Uwe Rudolph, M.D., of *McLean Hospital/Harvard Medical School*, will investigate the pathways that are disrupted in depression. Specifically, he will focus on the interplay between two neural signaling pathways: the GABAergic and glutamatergic systems, which, respectively, are inhibitory and excitatory. Using highly specific chemogenetic tools (genetically engineered proteins that interact with small molecules), he will explore how increasing the activity of GABA receptors affects biochemical signaling in the medial prefrontal cortex, a brain area required for decision-making and memory. Dr. Rudolph will also assess how modulation of GABA receptor function affects behavior in animal models of depression. This work will provide insight into a novel, potentially pharmacological pathway underlying depression.

Etienne L. Sibille, Ph.D., of the *Centre for Addiction and Mental Health, Canada*, is working to identify new molecular targets for drug development for depression. The majority of current drugs target a single molecular pathway, that of the neurotransmitter serotonin; little is known about other pathways that may contribute to the disease. Dr. Sibille will focus on defining the role of other signals in depression, such as somatostostatin (SST)-positive GABA neurons. He has found that reduced SST expression and function is associated with depression in both humans and animal models of the illness. He will explore how deficiencies in SST-positive neurons contribute to depression and assess whether modulation of these neurons is a potential avenue for antidepressant development.

Mental Illness–Multiple:

Richard Scott Jope, Ph.D., of the *University of Miami*, hopes to develop a potentially revolutionary new method to alter protein levels in the hippocampus, the center of learning and memory in the brain. Dr. Jope is using a potent class of signaling molecules known as siRNAs to control gene expression. He has found that, when administered through the nose, siRNAs accumulate in the hippocampus of mice. Dr. Jope plans to use this method to modulate the levels of genes that play an important role in a range of mental illnesses. His preliminary studies will focus on genes, such as GSK3 and histone deacetylases, that have been challenging to target with traditional methods. Dr. Jope hopes that his new method will produce highly targeted treatments with limited side effects for patients suffering from a wide variety of mental illnesses.

Kwang-Soo Kim, Ph.D., of *McLean Hospital/Harvard Medical School*, will work to identify the biological mechanisms that determine how a person reacts to trauma. For example, children who are exposed to abuse are much more likely to suffer from depression and addiction as adults. Still, a fraction of these children remain resilient despite their traumatic experiences. Using rodent models, researchers have gained insight into the hormone and chemical signaling that influence these behaviors. Dr. Kim now proposes to extend these findings to humans. Dr. Kim will generate stem cells from two groups of adult patients who were abused as children. One group will have a diagnosis of depression, while the other group will not exhibit any symptoms of mental illness. The stem cells from people in each group can be coaxed to form any adult neural cell type, thus enabling Dr. Kim to attempt to define the molecular, cellular, and physiological properties that underlie biological resilience.

Andres V. Maricq, M.D., Ph.D., of the *University of Utah*, will study how an auxiliary protein influences the function of a key neuronal receptor, called the NMDA receptor that is critical for learning and memory. This receptor has been implicated in numerous mental illnesses, including autism spectrum disorders, depression, Alzheimer's disease and schizophrenia, which make it an attractive target for new therapies. Dr. Maricq is working to understand how the receptor is regulated in an effort to identify additional avenues for drug development. Dr. Maricq has identified a protein known as NRAP-1 that is required for NMDA activity. He has proposed to define how NRAP-1 biochemically interacts with the NMDA receptor to control its activity. Dr. Maricq is hopeful that this work will lead to novel pharmacological therapies for diseases like depression and schizophrenia.

Marina R. Picciotto, Ph.D., of *Yale University*, will examine the role of an unstudied group of neurons in anxiety and depression. The so-called ChAT-positive neurons are a rare group of inhibitory cells in the hippocampus, the center of learning and memory in the brain. Dr. Picciotto hypothesizes that these neurons form an important network that is critical for oscillations in the hippocampus that lead to an increase in anxiety- and depression-like behaviors in rodents. Using a combination of molecular genetic, pharmacological, electrophysiological, and behavioral strategies, Dr. Picciotto will determine the effect of ChAT-positive neurons on neural signaling and behavior. The results will be the first functional and behavioral evaluation of this population in the hippocampus, and will provide a novel role for these neurons in behaviors related to anxiety and depression.

Gustavo X. Turecki, M.D., Ph.D., of *McGill University, Canada*, will study molecular changes in the brain that occur after severe child abuse. Children who have experienced these traumatic events are more likely to suffer from mental illnesses, including severe depression and addiction. Dr. Turecki will gather rare postmortem human brain samples to robustly and specifically characterize changes in the expression of genes and in chemical changes to DNA called methylation that are specifically associated with early-life adversity. He will focus on excitatory pyramidal neurons that are largely responsible for cognition. His goal is to improve our understanding of the molecular mechanisms underlying the impact of child abuse, and ultimately propose novel avenues for intervention.

Simon Keith Warfield, Ph.D., of *Children's Hospital, Boston*, will use innovative new technology to build structural maps of the connections between neurons in the developing fetal brain during pregnancy. Dr. Warfield has developed new technology that allows researchers to image the brain even while the fetus is moving. This motion-robust MRI and other imaging enables quantitative analysis of neural connections in the early brain. Using this technology, Dr. Warfield will analyze both healthy and at-risk fetal MRI cases. The at-risk population will include fetuses with identified maternal risk factors for developing mental health disorders, including those who have experienced stressful events during pregnancy or obstetric hypoxic complications. Dr. Warfield hopes motion-robust imaging will differentiate between abnormal and normal brain development, which will facilitate the identification of fetuses that are at risk for developing mental health disorders.

Post-Traumatic Stress Disorder:

Rachel Yehuda, Ph.D., of the *Icahn School of Medicine at Mount Sinai*, seeks to understand the neurobiological mechanisms involved in resilience to trauma and to define markers that will allow researchers to predict how a person will respond to trauma. Dr. Yehuda has identified neuroendocrine (hormonal) and molecular predictors of resilience and markers of recovery from PTSD. Now, she will examine these predictors in combination with markers of brain structure and function. Dr. Yehuda will scan 15 trauma-exposed individuals with PTSD and 15 trauma-exposed individuals without PTSD. Her goal is to identify neural circuits associated with resilience to trauma as well as neuroimaging biomarkers of treatment response to cognitive therapy in PTSD. More broadly, Dr. Yehuda hopes that improved biomarkers for a patient's response to trauma or the treatment of trauma will advance our understanding of the molecular mechanisms that underlie behavior.

Schizophrenia:

Beng-Choon Ho, M.D., of the *University of Iowa*, will work to develop a method to measure neuroinflammation in neuropsychiatric disorders. Dr. Ho will test a diagnostic known as advanced diffusion magnetic resonance imaging (dMRI) to determine if it can serve as a marker of brain immune activation triggered by obstetric complications. The work will take advantage of a unique and highly informative Dutch birth cohort which has been evaluated from prenatal life until mid-adolescence and is still ongoing. The project holds the promise to advance our knowledge of the mechanisms that govern neuroinflammation and provide insight into how maternal infections increase schizophrenia susceptibility, which may allow for earlier intervention and the development of improved therapeutics.

Elliot Hong, M.D., of the *Maryland Psychiatric Research Center*, hopes to build a comprehensive map of the brain based on both biochemical interactions and electrical signals. Our current understanding of the brain is largely derived from discrete maps that are based on unrelated structural, functional, chemical or electrical information. Yet complex diseases, like schizophrenia, are likely caused by defects in multiple pathways at once. Using a combination of technical and conceptual advances, Dr. Hong proposes to create the first large-scale map of the brain's synchronized electro-chemical dynamics. His hope is that this integrated image of the brain will provide insight not only into how chemical signals regulate neural activity, but will also identify abnormalities and network-dysfunctions that are commonly observed in patients with schizophrenia.

Neal R. Swerdlow, M.D., Ph.D., of the *University of California, San Diego*, will work to test an alternative approach to treating schizophrenia. For more than 50 years, antipsychotic drugs have been the main therapy for patients with schizophrenia, but these treatments often fall short in treating various cognitive aspects of the illness. Recent research suggests that patients may benefit from so-called pharmacologically augmented cognitive therapies (PACTs), which pair targeted drugs with cognitive therapies. The dual treatment may have synergistic effects. Dr. Swerdlow will treat schizophrenia patients with range of doses of the pro-attention psychostimulant, d-amphetamine, in addition to conventional antipsychotics. The drug treatment will be paired with cognitive therapy that is specifically targeted to develop attention skills. Dr. Swerdlow hopes that this investigation will provide compelling data that expands the use of PACTs to treat schizophrenia.

Dawn I. Velligan, Ph.D., of the *University of Texas Health Science Center at San Antonio*, will look for new biomarkers that are associated with particularly severe cases of schizophrenia. These markers will be used to assess a new treatment, known as the MOtiVation and Engagement (MOVE) Program. The method builds on existing therapies with comprehensive, home-based, multi-modal approaches, and results have been promising so far. Dr. Velligan will focus on inflammatory markers as potential biomarkers. He will examine the relationship between the amount of inflammatory markers circulating in the blood of patients and the severity of their negative symptoms. Dr. Velligan will also assess the impact of MOVE on levels of these molecules. This work has the potential to uncover novel biomarkers associated with the negative symptoms of schizophrenia, which may offer a path to more targeted, improved treatments.

For a more extensive summary of Distinguished Investigator projects, visit: http://bit.ly/2gZwurK.

About the Brain & Behavior Research Foundation

The Brain & Behavior Research Foundation is committed to alleviating the suffering of mental illness by awarding grants that will lead to advances and breakthroughs in scientific research. The Foundation funds the most innovative ideas in neuroscience and psychiatry to better understand the causes and develop new ways to treat brain and behavior disorders. These disorders include depression, bipolar disorder, schizophrenia, autism, attention-deficit hyperactivity disorder, anxiety, borderline personality disorder, obsessive-compulsive disorder, and post-traumatic stress disorder. Since 1987, the Foundation has awarded more than $360 million to fund more than 5,000 grants to more than 4,000 leading scientists around the world. This has led to over $3.5 billion in additional funding for these scientists. The Foundation is also dedicated to educating the public about mental health and the importance of research, including the impact that new discoveries have on improving the lives of those with mental illness, which will ultimately enable people to live full, happy and productive lives. For more information, visit www.bbrfoundation.org.