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 Vanderbilt Medical Center

Center to focus on brain's gene networks

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by Leigh MacMillan

Neuroscientists at Vanderbilt University are stepping into the national limelight with the establishment of a Silvio O. Conte Center for Neuroscience Research.

The new center, funded by a \$10 million grant from the National Institute of Mental Health (NIMH) and administered through the Center for Molecular Neuroscience, will support interdisciplinary studies aimed at understanding the gene networks that control serotonin systems in the brain.

The neurotransmitter serotonin is central to brain biology: it participates in systems that control sleep, aggression, sexual drive, satiety, reward and mood. Serotonin has been implicated in a range of disorders including depression, obsessive-compulsive disorder, schizophrenia and autism, and medications that affect serotonin signaling, such as the SSRI (selective serotonin reuptake inhibitor) antidepressants, are widely prescribed.

The Vanderbilt Conte Center investigators are focusing their efforts on the raphe nuclei, a cluster of serotonin neurons that reside in the brain stem and receive input from and send messages to neurons throughout the rest of the brain.

"This is one of the most medically important cell groups in the nervous system, and the genes that control these neurons and their output are particularly key to our understanding of mental illness risk," said Randy Blakely, Ph.D., director of the new Conte Center.

"Dr. Blakely has assembled the right team for the job of understanding how genetic variability affects neurotransmitter systems in the developing brain," said Thomas Insel, M.D., director of the NIMH. "The new Center holds promise for hastening the day when discoveries in the lab will be translated into improved treatments for people with mental illnesses, from mood disorders to autism."

Conte Centers for Neuroscience Research are a centerpiece of NIMH funding, said Beth-Anne Sieber, Ph.D., chief of the Developmental Biology Program at NIMH. "With these centers, NIMH is looking to the investigators to push their hypotheses forward, create new hypotheses, and find answers relevant to mental health."

"The Vanderbilt center is the epitome of a Conte Center," she said. "It really captures the spirit of integration and synergy between investigators."

The centers are named for the late U.S. Rep. Silvio O. Conte, a longtime advocate for scientific research and organizer of the 1990s "Decade of the Brain" efforts. There are approximately 10 Conte Centers for Neuroscience Research and 10 Conte Centers for the Neuroscience of Mental Disorders — centers with a translational-clinical research emphasis.

Blakely said the new center reflects Vanderbilt's commitment to and investments in neuroscience programming, evident in the growth in research and education here over the last decade.

"This is a defining moment for the neurosciences at Vanderbilt," said Jeffrey Balser, M.D., Ph.D., associate vice chancellor for Research. "Over the last few years, we have received several forms of external validation that affirm neuroscience at Vanderbilt has become absolutely top tier. An NIH Conte award makes that excellence even more visible to the national and international research community, and at the same time will provide crucial resources for making fundamental progress in mental health research."

The Vanderbilt Conte Center includes scientists from the School of Medicine and the College of Arts and Science as well as researchers at other institutions. The center investigators will probe the workings of serotonin neurons in the raphe complex from their earliest stages of development to their function in mature animals. The operating hypothesis of the group, Blakely said, is that a rich network of genes establishes and maintains serotonin signaling in the brain and that deficits in the formation or stability of this network in humans underlies risk for mental illness.

The projects make extensive use of specialized mouse models, including mice in which serotonin neurons have been specifically tagged with fluorescent marker proteins or have had selective changes to their serotonin signaling molecules.

"We know that serotonin networks — broadly, all the genes that cooperate to control serotonin assembly and signaling — can be identified and manipulated in the mouse," Blakely said, "and we feel strongly that the

conservation of these networks in humans will allow us to formulate new hypotheses regarding disease-associated genetic variation.”

The Conte Center will also support multiple core facilities that “rest upon the significant technological framework that has been established at Vanderbilt through its shared resources program,” Blakely added.

For example, a new Biobehavioral Core, led by Danny Winder, Ph.D., will spark the expansion of the existing Murine Neurobehavioral Core, with plans to move the facility to dedicated space above the Imaging Institute next year. Other cores include the Administrative Core, led by Blakely; a Bioanalytical Core, led by Ariel Deutch, Ph.D.; and a Bioinformatics/Biostatistics Core, led by Jay Snoddy, Ph.D.

In addition to its core facilities that will benefit the wider Vanderbilt research community, the Conte Center will administer a pilot grant program targeted to young investigators or established investigators who wish to enter the field of serotonin biology. The center will also host an annual symposium centered on the themes of the Conte program, and Conte Center members will participate in outreach activities that convey to a broader audience the “why” behind the research.

PROJECTS AND LEADERS

Randy Blakely, Ph.D. — Signaling networks sustaining serotonin transport

Presynaptic serotonin transporters control serotonin availability by clearing it from the synapse and recycling it for future release. Serotonin transporters are targets for the most commonly prescribed antidepressant medications, and genetic variation in these molecules has been linked to autism, anxiety, major depressive disorder and antidepressant response. Blakely first identified the gene that encodes the serotonin transporter more than 15 years ago. His team will investigate the protein network that regulates the serotonin transporter.

Pat Levitt, Ph.D. — Serotonin modulation of axon guidance during brain development

In addition to its role in neuronal signaling in the adult brain, serotonin appears to act very early in development to help shape the brain's circuitry. Variations in serotonin system genes are associated with neurodevelopmental disorders, such as autism. Levitt and colleagues have identified a novel role for serotonin in modulating the signaling of axon guidance molecules. The investigators will explore how serotonin impacts the

trajectories of axons to their targets, particularly in two key circuits involved in mental health disorders: thalamocortical axons and dorsal raphe axons.

Elaine Sanders-Bush, Ph.D. — Genetic variation of murine serotonergic phenotypes

Recombinant-inbred (RI) mouse strains have become useful tools for dissecting how combinations of genetic variants contribute to a functional phenotype. Sanders-Bush and colleagues will use RI mice to examine how genetic variation in genes that control serotonin production, signaling and reuptake contribute to biochemical and behavioral phenotypes. This approach will allow the investigators to examine the impact of a spectrum of genetic variation and also to identify new genes that control serotonin signaling.

Ronald Emeson, Ph.D. — Modulation and function of serotonin-2C receptors

The serotonin-2C receptor has been implicated in a number of human psychiatric and behavioral disorders. Studies from the Emeson and Sanders-Bush laboratories were the first to demonstrate that a novel RNA modification process called RNA editing modulates the function of the serotonin-2C receptor. RNA editing can produce as many as 24 different serotonin-2C receptor isoforms, which may serve as a mechanism for regulating serotonin signaling. Emeson and colleagues will elucidate the brain region-specific pattern of serotonin-2C receptor editing and explore the physiologic and behavioral relevance of the different receptor isoforms.

Douglas McMahon, Ph.D. — Interactions of serotonin and circadian signaling networks

The master circadian (daily biological rhythm) pacemaker of the brain, the suprachiasmatic nucleus, receives direct input from serotonin neurons, and in turn, sends signals to other serotonin neurons. McMahon and colleagues will examine how circadian rhythms control the properties of serotonin neurons, and how serotonin impacts circadian behavior. The investigators propose that serotonin and circadian systems are interlocked and that perturbation in one system affects the function of the other, resulting in behavioral alterations associated with human affective disorders.

Evan Deneris, Ph.D., Case Western Reserve University — Genetic networks establishing serotonergic neuronal identity

Because serotonin neurons are difficult to access, only a small number of the genes that contribute to their developmental program has been identified to

date. Deneris and colleagues have developed transgenic mice that selectively express fluorescent proteins in serotonin neurons, enabling direct access to these neurons for gene expression studies. Investigators will use serotonin neuron-specific gene manipulation to explore the function of these genes in vivo.