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VU319: The academic difference

By Bill Snyder

Earlier this year, researchers at Vanderbilt University reported tantalizing results from a Phase 1 trial in humans of a potential new drug—called VU319—that could transform the treatment of Alzheimer's disease and schizophrenia.

The story of VU319 is one of collaboration. Three of the principal players can be seen on the opposite page: Craig Lindsley (left), P. Jeffrey Conn, (center), and Carrie Jones.

Results of the study were reported this summer at the Alzheimer's Association International Conference, a virtual event this year due to COVID-19. This is an important step toward confirming that VU319 may improve cognitive functioning, including learning, memory and attention, in people who suffer from these devastating diseases.

The findings also represent a tour de force for an academic medical center, a collaboration between Vanderbilt's Warren Center for Neuroscience Drug Discovery, where the compound was discovered and optimized for activity in preclinical studies, and the Vanderbilt University Medical Center, where the compound was evaluated for safety in human testing.

"While there are other academic drug discovery groups, there's nothing like what's happening here, with the combination of deep basic science and a large team of people focused on one endgame—to continue to develop and deliver [potential new drugs] on a pipeline," said **Craig Lindsley**, William K. Warren, Jr. Chair in Medicine and professor of pharmacology and WCNDD's director of medicinal chemistry.

"There have been some bumps in the road but we've always managed to get over those bumps," added **Paul Newhouse**, the Jim Turner Chair in Cognitive Disorders, who led the clinical trial. "I remain very optimistic that this treatment approach could have a real impact on patients."

The Phase I study, which began in the summer of 2017, was designed primarily to evaluate VU319's safety, but it also incorporated a battery of cognitive and electroencephalography tests of brain function, which monitor and record electrical activity in the brain. Safety was excellent in individuals who received VU319, and, at the highest doses, the healthy participants showed evidence of enhancement on EEG measures of memory and attentional performance over levels at lower doses or while on placebo.

"I want to make my contribution to science," said one of the participants in the Phase I trial, Rhea-Anne Pendley, who is from Springfield, Tennessee. Pendley's mother died from dementia-related complications in 2017. "If I can help someone or even help myself along the way," she said, "that's worth it all."

The next step is to conduct extensive Phase II trials of VU319 in patients with Alzheimer's disease. As significant resources are required for such studies, Vanderbilt recently licensed VU319 to San Diego-based Acadia Pharmaceuticals for further clinical development.

Solving the puzzle

This model of drug discovery and development is the brainchild of the center's founder, **P. Jeffrey Conn**, who holds the Lee E. Limbird Chair in Pharmacology. "For me, brain disease has always been a passion, to see if systematically developing new approaches, each of which could be a breakthrough, could fundamentally impact patient care and patients' lives," he said.

Conn's passion began early. After watching his grandmother lose her memory to dementia, and after a close childhood friend was hospitalized for early-onset schizophrenia, this young man from Cleveland, Tennessee, resolved to try to do something to improve the treatment of brain disease.

Conn earned a doctorate from Vanderbilt in 1986, then joined the faculty at Emory University, where he began studying how the neurotransmitter glutamate affects brain function.

Neurotransmitters are molecules that carry signals between neurons. Most act by binding to protein receptors on the surface of the cell that will receive the signal. When something goes wrong with neurotransmitter binding or signaling, that's when disordered thinking, behavior, and function—brain disease—can occur. Many drugs that act to modulate brain function do so by modulating the function of neurotransmitter receptors.

Paul Newhouse

Conn became interested in Parkinson's disease, a movement disorder characterized by tremors, difficulty walking, and muscle weakness caused by the progressive loss of nerve cells that produce the neurotransmitter dopamine.

Current dopamine replacement therapy for Parkinson's disease improves normal motor function, but prolonged use of the drugs can cause significant side effects, and they become less effective as the disease progresses. This led Conn to wonder if it was

possible to treat the disease by "tweaking" pathways involving other neurotransmitters, notably glutamate.

In 2000, Conn accepted a position as senior director and head of the Department of Neuroscience at Merck Research Laboratories in West Point, Pennsylvania. There, he and his colleagues found that by activating $mGlu_4$, a specific glutamate receptor, they could relieve symptoms of Parkinson's disease in animals. However, there are multiple different types of glutamate receptors in the brain, and they could not find a compound that would bind only to $mGlu_4$ without activating these other receptors and causing unwanted effects.

That's when they hit upon "allosteric modulation" as a possible solution. This tongue twister refers to the ability of some compounds to bind to a secondary site on a receptor in a way that modulates its activation by the neurotransmitter. Think of the neurotransmitter as the key that unlocks the receptor's activity through their main binding sites, and of allosteric modulators as a dial that adjusts the intensity of the receptor's activation. Since secondary sites differ more widely that primary sites among different receptors for a single neurotransmitter, it is easier to find an allosteric modulator that is selective for only one type of receptor, such as $mGlu_4$.

Within a couple of years, Conn and his team had discovered an allosteric potentiator—a modulator that increases a receptor's activity—that was specific for $mGlu_4$. But Conn knew it would be difficult to secure the time and resources needed to validate—through laboratory and animal testing—the therapeutic potential of his "high-risk" idea in a corporate environment.

Building a winning team

At about the same time, Vanderbilt was making a significant investment in early-stage drug discovery by creating the Vanderbilt Institute of Chemical Biology. Seeing an opportunity to advance his research, Conn moved his lab to Vanderbilt in 2003.

"As drug discovery has become more automated and technology driven, it's really a matter of being able to afford the technology and having a culture of collaboration," Conn said at the time. "This is not out of range for a university like Vanderbilt that has a tradition of investing in big science."

In 2006, Lindsley, who'd worked with Conn at Merck and was a pioneer in discovery of the early allosteric modulators of neurotransmitter receptors, came aboard as director of medicinal chemistry. "The ability to recruit someone of Craig's caliber to Vanderbilt represented a real milestone that allowed us to begin to execute full industry-standard drug discovery efforts", said Conn.

Others who joined Conn's team and the Vanderbilt faculty during this period included **Colleen Niswender**, a research professor of pharmacology and now the WCNDD director of molecular pharmacology, and **Carrie Jones**, associate professor of pharmacology and WCNDD director of behavioral pharmacology.

By early 2008, the researchers had reported the discovery of highly selective allosteric modulators that could independently ramp up the activity of two receptors for the neurotransmitter acetylcholine—M_1 and M_4. Based on animal studies, the discovery raised hopes that new, more specific and more effective treatments for brain diseases like schizophrenia and Alzheimer's disease were now within reach. This work led to the discovery of VU319, an allosteric modulator of M_1.

The academic difference

Through the Vanderbilt Center for Neuroscience Drug Discovery, which was established in 2011, the researchers received substantial support from the NIH; AstraZeneca, a global biopharmaceutical company; Janssen Pharmaeutica, a Johnson & Johnson company; and the Michael J. Fox Foundation for Parkinson's Research.

The center also got a big boost from the William K. Warren Foundation of Tulsa, Oklahoma, which supports research aimed at improving the treatment of schizophrenia and other forms of serious mental illness. Thanks to continued support and a sustained partnership, in May of this year it was reestablished as the Warren Center for Neuroscience Drug Discovery.

The size of a small biotechnology company, the Warren Center receives approximately $20 million in corporate and government funding each year to support the work of 100 full-time faculty and staff scientists, postdoctoral fellows, and graduate students.

Close behind VU319 are several more potential drugs in various stages of testing and development for the treatment of Parkinson's disease, schizophrenia, depression, Rett syndrome, and other brain disorders.

"It's really unprecedented for an academic group to have a pipeline with multiple targets that are moving forward," Conn added. Because researchers in academia can spend more time studying the effect of their compounds on brain function, "we hope

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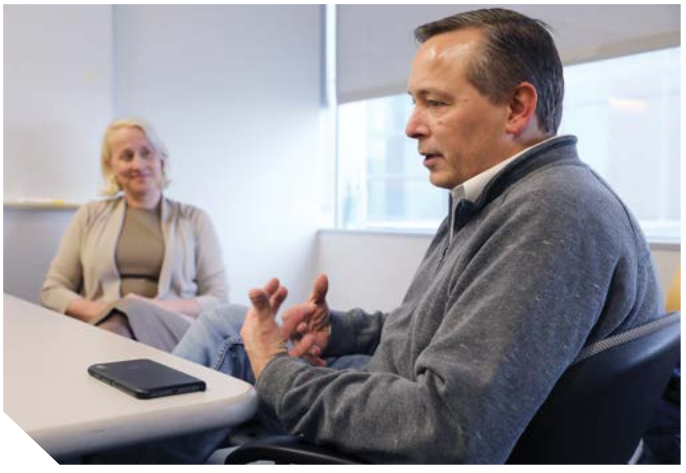

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we're developing better drugs…with a higher chance of going the distance," he said.

"In industry you'd have 18 months to 2 years to start a program from scratch and get a candidate and move on," Lindsley explained. "And time and time again we'd see those [programs] fail because you didn't have the time to understand the compound well enough to design a target for it.

"Here we can spend five to six years doing the basic science, understanding what a candidate compound should look like, and developing the candidate that really is going to be ideal for that target with the right efficacy and safety," he said. "It's the ideal situation."

That doesn't mean road to the Phase 1 trial of VU319 was an easy one to travel.

Clinical trials are highly regulated by the US Food and Drug Administration. "Universities aren't necessarily set up to handle all of the regulatory burden and they don't necessarily have all the systems in place for making sure…that all that data and all those processes pass FDA muster," Newhouse said.

Fortunately, the Warren Center had a lot of help, including from:

- The **Center for Cognitive Medicine** at VUMC, which ran the Phase 1 trial;
- The **Vanderbilt Coordinating Center**, which supports clinical and translational research throughout the medical center;
- The **Investigational Drug Service**, a team of specially trained pharmacists and certified pharmacy technicians within the VUMC Department of Pharmaceutical Services that supports human clinical research involving investigational products;
- The **Vanderbilt Clinical Research Center**, an inpatient and outpatient research facility dedicated to conducting clinical research patient care; and
- The **Vanderbilt Institute for Clinical and Translational Research**, a comprehensive resource for researchers and clinicians supported by VUMC's Office of Research and by a Clinical and Translational Science Award from the NIH.

"We couldn't have done this without everyone pitching in," Newhouse said. "It's very much a cross-institutional effort."

Support from the Warren Foundation enabled the researchers to conduct safety studies of VU319, as required by the U.S. Food and Drug Administration before granting an investigational new drug application to conduct human trials.

The Phase 1 trial received substantial support from the Alzheimer's Association and its Part the Cloud program, which aims to accelerate critically needed Alzheimer's disease research, and from the Alzheimer's Drug Discovery Foundation in New York.

"That's what you need for this kind of work in academics," Lindsley said. "You've got to have some philanthropy."

That, and passion.

"We're realizing a lifelong quest," said Conn. "Many of us come into science because we want to make an impact on human health…We're not satisfied would with the status quo…We want to change things in a positive way."

$20M gift establishes new Warren Center for Neuroscience Drug Discovery

Vanderbilt University received $20 million from The William K. Warren Foundation in Tulsa, Oklahoma, to establish the Warren Center for Neuroscience Drug Discovery, formerly known as the Vanderbilt Center for Neuroscience Drug Discovery.

The William K. Warren Foundation was founded in 1945 by oilman William Kelly Warren and his wife, Natalie Overall Warren, who graduated from Vanderbilt (1920) and shares that distinction with her father (1885) and her four siblings. The Warren Foundation established Oklahoma's largest health care provider, the Saint Francis Health System, and the Laureate Institute for Brain Research in Tulsa. The Foundation supports health care innovation, medical research, Catholic initiatives, education, and Tulsa-specific causes.

"We have been impressed with the creative approaches and hard work demonstrated by Vanderbilt researchers, especially Craig [Lindsley] and Jeff [Conn], in the Center for Neuroscience Drug Discovery," says John-Kelly Warren, CEO of the Warren Foundation and grandson of the founders. "Supporting novel, research-based methods to combat devastating cognitive impairments and mental illnesses lies at the heart of our foundation's mission. It is also gratifying to support this research at Vanderbilt University, an institution that has made a significant impact on the lives of so many, including my family."

John-Kelly Warren

In addition to supporting research efforts, part of the Warren gift will be used to create an endowment designed to encourage mentorship and the development of a long-term pipeline of research leaders.

In addition to this latest commitment, the Warren Foundation has been a longstanding supporter of Vanderbilt and its Center for Neuroscience Drug Discovery. Seven endowed faculty chairs currently are supported by the foundation—ranging in disciplines from medicine and pediatrics to divinity—and the William K. Warren Foundation Scholarship is awarded to deserving undergraduates in the College of Arts and Science. **— Ryan Underwood**