

# Turning science into progress

**Professor Jeffrey Conn** discusses the structural problems that hinder advances in new drug treatments and how an innovative neuroscience drug discovery centre in the US is bridging the gap between basic research and industrial development



**You are Principal Investigator of the Jeffrey Conn Research Group and Director of the Vanderbilt Center for Neuroscience Drug Discovery (VCNDD). Why did you establish the Center?**

I moved to Vanderbilt from Merck in 2003 to establish this effort. When working in an industry setting, I became increasingly concerned that a major gap existed between academic and industry research. While scientists in academic and other basic science settings have made tremendous progress in furthering our understanding in biology, chemistry and related disciplines, they often

fail to make the critical link that allows this information to be useful in an industrial setting. Likewise, fiscal pressures that govern research efforts in industry settings make it increasingly difficult for companies to invest significant resources in exploratory projects that capitalise on translating cutting-edge discoveries of basic science into marketable products.

**How does the VCNDD respond to this disconnect in research?**

The most innovative and high impact advances in therapeutics are likely to come from aggressive efforts to provide a bridge that allows translation of advances in basic science to novel therapeutics and marketable products. I felt that it was critical to establish new models to fill this gap. I realised that this could only be accomplished by establishing the infrastructure, expertise and culture in major academic research centres to fully advance novel ideas and approaches to a level where pharmaceutical companies could invest the major capital required to take a new drug candidate through development and to the market. The VCNDD helps meet this critical need.

**What sets the VCNDD apart from other organisations, and how has this helped to aid the drug discovery process?**

We are fundamentally different from drug companies in that we prioritise and invest in blending drug discovery with the highest quality of basic research. All of our drug discovery efforts are intermeshed with intense basic science efforts in which we endeavour to fully understand the drug targets we study, subtle differences in drug leads that act on these targets and fundamental neuroscience that is essential to understanding the actions of our drug candidates. We are also fundamentally different from most academic labs in that we possess the expertise and infrastructure for drug discovery, traditionally only found in industry settings, to optimise high quality drug candidates that are suitable for moving into clinical development.

**What hurdles are there to the translation of basic science research into treatments?**

For brain disorders, 70 per cent of new drug discovery efforts fail because of lack of efficacy in late clinical testing. It is critical that we become more sophisticated in selecting and validating new drug targets and ensuring that the drug reaches its target in the brain. In many cases, we do not fully understand the disease and role of the drug target in the disease process. We must develop a better understanding of the basic underpinnings of brain disorders and become better at selecting appropriate targets based on that understanding.

The emergence of organisations such as the Vanderbilt Center for Neuroscience Drug Discovery signals a shift in the drug development model, blurring traditional boundaries to draw new objectives into the work of academic scientists

## Lost in translation

Despite major advances in our understanding of neurological and psychiatric disorders in recent years, pharmaceutical agents to treat them have some way to catch up. The **Vanderbilt Center for Neuroscience Drug Discovery** in Nashville, Tennessee, USA provides a novel remedy for realigning understanding and treatment

Related to this is the issue of patient selection for clinical trials. Historically, companies have preferred wide patient categories to allow a broad label for a new drug. However, we now appreciate that most clinically defined brain disorders are actually a collection of multiple disorders, each with a different aetiology and mechanistic underpinning, but which manifest in similar symptoms.

### How can we improve the usefulness of clinical trials?

We must understand the differences between brain disorders, develop drugs for more clearly defined patient subpopulations, and focus our clinical trials on the patients for which the drug is most likely to have greatest efficacy. Even with these efforts, there have been many instances in which clinical trials fail to demonstrate efficacy, and we lack data to clearly establish that the drug candidate got into the brain and gained access to the target. In these cases, we do not know if the trial failed because the target is not viable or because the drug did not reach its target. We must get better at measuring the ability of the drug to interact with the target in the human brain in order to remove this source of failure and uncertainty. While we have improved at this, we need to continue to develop better biomarkers of drug action in the brain.

**IN RECENT YEARS**, scientists have made major advances in understanding common brain disorders such as Alzheimer's, Parkinson's, schizophrenia and depression, yet this new knowledge has not been accompanied by equal progress in the development of novel drugs to treat them. A large number of today's medications were discovered decades ago, or represent only slight modifications to old medicines, with improved efficacy or reduced side effects.

If researchers are to make the necessary strides to make a real difference to those affected, completely novel molecules must be derived from our bottom-up knowledge of the diseases they must treat. Unfortunately, the normal drivers of drug development – pharmaceutical companies – are often reluctant to invest in fundamentally new approaches due to the high financial risk associated with investment in new approaches that are not fully validated. In contrast, universities have traditionally been more focused on the basic science behind disorders rather than the actual development of treatments.

### BRIDGING THE GAP

The gap between advances in understanding and therapy development reflects this diversion in perspective between academia and industry. Finding a way to bridge this separation, through the translation of advances in neuroscience into practical solutions, should lead to more rapid delivery of treatments. This is the aim of the Vanderbilt Center for Neuroscience Drug Discovery (VCNDD), directed by Professor Jeffrey Conn in Nashville, Tennessee, USA.

The organisation focuses on the development of new medications for multiple brain disorders, including Parkinson's, Alzheimer's, schizophrenia, depression and autism spectrum disorders. Recognising the financial risk of investment in novel drugs, the aim of the Center is to 'de-risk' R&D investments made by pharmaceutical companies for developing such drugs. The VCNDD achieves this by fully integrating basic academic research into the drug discovery process to optimise new drug candidates that are promising enough to be taken on by pharmaceutical companies, as Conn explains: "This allows us to develop a much greater understanding of the potential viability of new drug targets and develop the molecules and datasets needed for companies to invest in a new effort".

### BEST OF BOTH WORLDS

The VCNDD combines the aims and techniques of university and industrial laboratories. It brings the infrastructure and expertise from industry into an academic setting which enables researchers to apply high-throughput screening of compounds, medicinal chemistry, and drug disposition science to optimise molecules suitable for use as drugs. Center scientists carry out drug discovery efforts while maintaining an academic focus on the basic science understanding of the disorders and effects of novel molecules on signalling in the brain. By concentrating on understanding the diseases, novel approaches to treatment can be found which would be obscured by a purely drug-led approach. Using this approach, the Center has published 276 papers, building the collective knowledge-base of neurological diseases and the viability of

## INTELLIGENCE

### VANDERBILT CENTER FOR NEUROSCIENCE DRUG DISCOVERY

#### OBJECTIVES

To take the most exciting advances in the understanding of human disease and drug targets to a point where these breakthroughs can directly impact patient care.

#### KEY TEAM MEMBERS

**Dr Colleen Niswender**, Molecular Pharmacology; **Dr Craig Lindsley**, Medicinal Chemistry; **Dr Scott Daniels**, Drug Metabolism and Pharmacokinetics; **Dr Carrie Jones**, Behavioral Pharmacology

#### FUNDING

National Institutes of Mental Health (NIMH) • Alzheimer's Association • National Institute of Neurological Disorders and Stroke • National Institute of Drug Abuse • NIH Common Fund – Molecular Libraries and Screening Center Network • Johnson & Johnson • Michael J Fox Foundation • Alzheimers Drug Discovery Foundation • Thome Memorial Foundation • PhRMA Foundation • National Alliance for Research on Schizophrenia and Depression (NARSAD) • National Institute of Drug Abuse • Seaside Therapeutics • Astrazeneca • Bristol Myers Squibb

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**PROFESSOR JEFFREY CONN** received his BS in Psychology from Lee University in 1981 and PhD in Pharmacology from Vanderbilt University in 1986. He pursued postdoctoral studies in the Department of Pharmacology at Yale University until, in 1988, he joined the Department of Pharmacology at Emory University, where he rose to the rank of Full Professor. Conn moved to Merck & Co. in 2000 to assume the position of Senior Director and Head of the Department of Neuroscience. In 2003, he moved to Vanderbilt University to start a new Program in Drug Discovery, which is now the Vanderbilt Center for Neuroscience Drug Discovery (VCNDD).

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compounds to treat them, whether or not this leads to the actual development of medicines.

In identifying candidate molecules, the VCNDD is part of a shift in universities to fill the void created by the downscaling of industrial research into psychiatric and neurological disorders. The development of medications for these conditions is particularly costly due to the particularities of drug delivery to the brain. Medication must cross the blood-brain barrier, which has evolved to prevent foreign substances from traversing it. As the majority of brain conditions are chronic, there is the added complication that the drug must be regularly taken over a long period of time, widening the opportunity for harmful side-effects. As such, there is higher US Food and Drug Administration (FDA) scrutiny, and development times are longer, increasing costs. R&D projects in neurological research are thus often the first to be axed during financially straitened times.

#### COLLABORATIVE ACHIEVEMENT

The Center has already had much success in bench-to-bedside R&D, with 270 patents and seven drug partnerships to date. Although none of their efforts have yet reached clinical testing, many are in preclinical development as the VCNDD works with industry partners to develop animal toxicity testing required by the FDA before human trials can commence.

In September 2012, the VCNDD and Bristol-Myers Squibb announced a partnership in the development of glutamate-based drug candidates for the treatment of Parkinson's disease. Earlier this year, the Center licensed to AstraZeneca the rights to molecules that act on muscarinic acetylcholine receptor M4 for the treatment of many neurological disorders. In turn, in a longer-term collaboration the pharmaceutical company will provide funding to the VCNDD to continue investigations into these compounds.

Such partnerships are fundamental to the Center because, as a new enterprise, it cannot rely solely on the traditional pathways of university

funding. The majority of VCNDD funds come from the National Institutes of Health (NIH). Other funding is targeted at the development of specific compounds and is provided by organisations such as the Michael J Fox Foundation, which funds research into Parkinson's disease, as well as from industry partners such as AstraZeneca and Johnson & Johnson.

#### DIVERSE DISCOVERY

The work of the VCNDD is diverse, with approximately 100 members divided into four Discovery Teams, each directed by world leaders in their respective disciplines: Medicinal Chemistry, led by Dr Craig Lindsley; Molecular Pharmacology, led by Dr Colleen Niswender; Drug Metabolism and Pharmacokinetics, headed by Scott Daniels; and Behavioral Pharmacology, directed by Dr Carrie Jones. To provide an example of one of the many threads of ongoing basic science research, one group studies the cellular and molecular mechanisms involved in the regulation of signalling in the central nervous system, focusing on the physiological roles of metabotropic glutamate receptors (mGluRs). Their investigations are revealing key regulatory proteins which hold promise as potential drug targets.

#### THE FUTURE MODEL

The emergence of organisations such as the VCNDD signals a shift in the drug development model, blurring traditional boundaries to draw new objectives into the work of academic scientists. These organisations have the potential to direct much-needed earnings from drug sales by large pharmaceutical companies to the academic institutions that discover novel compounds. The adoption of some industry R&D roles by academic organisations and close collaboration between industry and academia has the potential to generate monetary reward for both. Most importantly, the VCNDD pays testament to the ability of these public-private partnerships to foster innovation, driving the development of treatments that will have a real impact on the lives of many.



Left to right: Colleen Niswender, Jeff Conn, Craig Lindsley, Scott Daniels (sitting) and Carrie Jones.