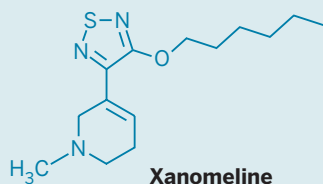


# ANATOMY OF AN ACADEMIC DRUG DISCOVERY PROGRAM

Inventing new medicines inside university walls requires **COMPLEX FUNDING** and a highly collaborative research plan

LISA M. JARVIS, C&EN CHICAGO



## MID-1990S Eli Lilly & Co.'s

xanomeline, an agonist of M1 muscarinic receptors, is shown to reduce agitation and improve cognition in people with Alzheimer's disease, but unpleasant side effects cause more than half of the clinical study participants to drop out. Lilly halts Alzheimer's studies for the drug.

**2000–03** While head of neuroscience at Merck & Co.'s West Point, Pa., site, **P. Jeffrey Conn**, intrigued by the Lilly data, tries but fails to convince management to pursue positive allosteric modulators (PAMs) of M1 and M4 muscarinic receptors.

**2003** Conn joins Vanderbilt University to start what will become the Vanderbilt Center for Neuroscience Drug Discovery (VCNDD).

## 2003 The National Institutes of Health

introduces National Cooperative Drug Discovery/Development Groups for the Treatment of Mood Disorders or Nicotine Addiction. The program, led by the National Institute of Mental Health (NIMH) and other institutes, creates an avenue for academic labs to secure financial support for drug discovery that otherwise would have been difficult to fund through the government.

**2004** NIH's Roadmap for Medical Research is introduced, laying the groundwork for grants to support high-throughput screening and medicinal chemistry activities.

**ACADEMIC INSTITUTIONS** are increasingly formalizing their efforts to discover new drugs, often by establishing centers that bring together researchers and technology from across disciplines. As their ranks grow—the nonprofit Academic Drug Discovery Consortium now counts 94 centers as members—a question arises: What does it really take for an academic institution to invent a viable drug candidate?

To answer that question, C&EN looked at efforts by the Vanderbilt Center for Neuroscience Drug Discovery (VCNDD) to develop a series of small molecules to treat brain disorders. That program, ultimately licensed to AstraZeneca, reveals the complexity of assembling the funding and scientific know-how needed to bring an invention to the point that it can be handed

off to an experienced drug developer.

The early-2013 deal with AstraZeneca for compounds acting on the M4 muscarinic acetylcholine receptor, a biological target relevant in schizophrenia and Alzheimer's disease, was the culmination of eight years of work by the VCNDD team. The team's research was supported by seven government grants that, along the way, generated 50 publications related to the biology and chemistry of modulating the M1 and M4 receptors.

Such success for an academic drug discovery center is impressive, but few have the resources of VCNDD. Formally established in 2007, the center has grown to include roughly 100 full-time employees. In 2013, VCNDD's budget topped \$20 million, more than half of which came from the National Institutes of Health. Corporate partners—which include AstraZene-

ca, Johnson & Johnson, and Bristol-Myers Squibb—contributed most of the rest.

VCNDD's funding stream took years of thoughtful planning and intense teamwork to assemble. Also enabling the work were new grants introduced by NIH and an increased focus by the National Institute of Mental Health to support research that bridges basic science and drug development, according to VCNDD's director, P. Jeffrey Conn.

Conn says his best advice for universities formalizing their drug discovery efforts is to avoid a contract research model, in which core facilities are available to individual researchers, in favor of a dedicated team of drug hunters. "It really does take a very focused team effort in which every member of the team is intellectually fully invested in—obsessing day and night about—the project," Conn says. ■

**2006 Conn** is awarded an X01 grant through NIH's Molecular Libraries Program to screen for selective PAMs of M1 at an NIH center.

**2006 Colleen Niswender**, VCND's director of molecular pharmacology, is awarded an X01 grant through NIH's Molecular Libraries Program to screen for selector PAMs of M4 at an NIH center.

**2005 Conn** wins an R01 grant from NIMH to study the science of muscarinic receptor activators as potential antipsychotic drugs. Funding through 2013 totals **\$2.9 million**.

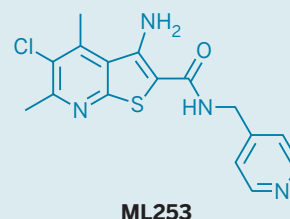
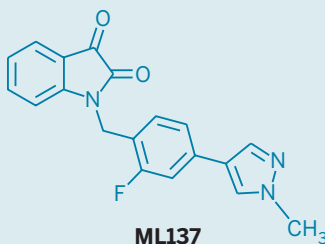
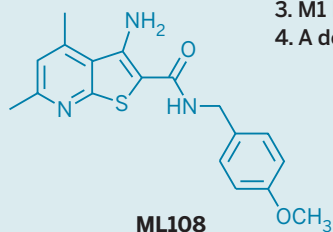
**2008 Craig Lindsley**, director of medicinal chemistry at VCND, is awarded an R01 grant from NIMH to develop selective M1 allosteric modulators for the treatment of schizophrenia. Funding totals **\$1.7 million**.

**2008 Lindsley** is awarded a U54 grant from NIMH to become part of an NIH network developing chemical probes, a research tool. The grant creates the Vanderbilt Specialized Chemistry Center for Accelerated Probe Development; overall funding is **\$25.5 million**. A small part of those funds are used to develop probes for M1 and M4.

**2009 Carrie Jones**, VCND's director of behavioral pharmacology, is awarded an R01 grant from NIMH to conduct animal studies of M4 PAMs as schizophrenia treatments. Total funding is **\$1.9 million**.

#### KEY DISCOVERIES FROM M1 AND M4 PROGRAMS (2009–10)

1. Allosteric agonists aren't optimal as drugs, but PAMs are suitable.
2. M4 PAMs impart an antipsychotic effect in rodents.
3. M1 PAMs enhance cognition in rodents.
4. A dozen M1 and M4 chemical probes are found (three shown).



**FEBRUARY 2012**  
**AstraZeneca** ends in-house neuroscience R&D in favor of a virtual model. VCND is among the first organizations it contacts as a possible partner.

**2010 Conn** gets a U01 grant from NIMH to establish the Vanderbilt National Cooperative Drug Discovery/Development Group for discovery of novel treatments for schizophrenia. The grant includes funds to optimize compounds. Funding through 2014 is **\$9.4 million**.

**SEPTEMBER 2011**  
VCND licenses glycine transporter 1 inhibitors for schizophrenia, developed with support by the U01 grant, to **Karuna Pharmaceuticals**.

**NOVEMBER 2013**  
VCND is in early discussions to license out M1 PAMs. A deal is expected in late 2014.

**JANUARY 2013** VCND and AstraZeneca form a partnership to develop M4 PAMs for the treatment of major brain diseases.