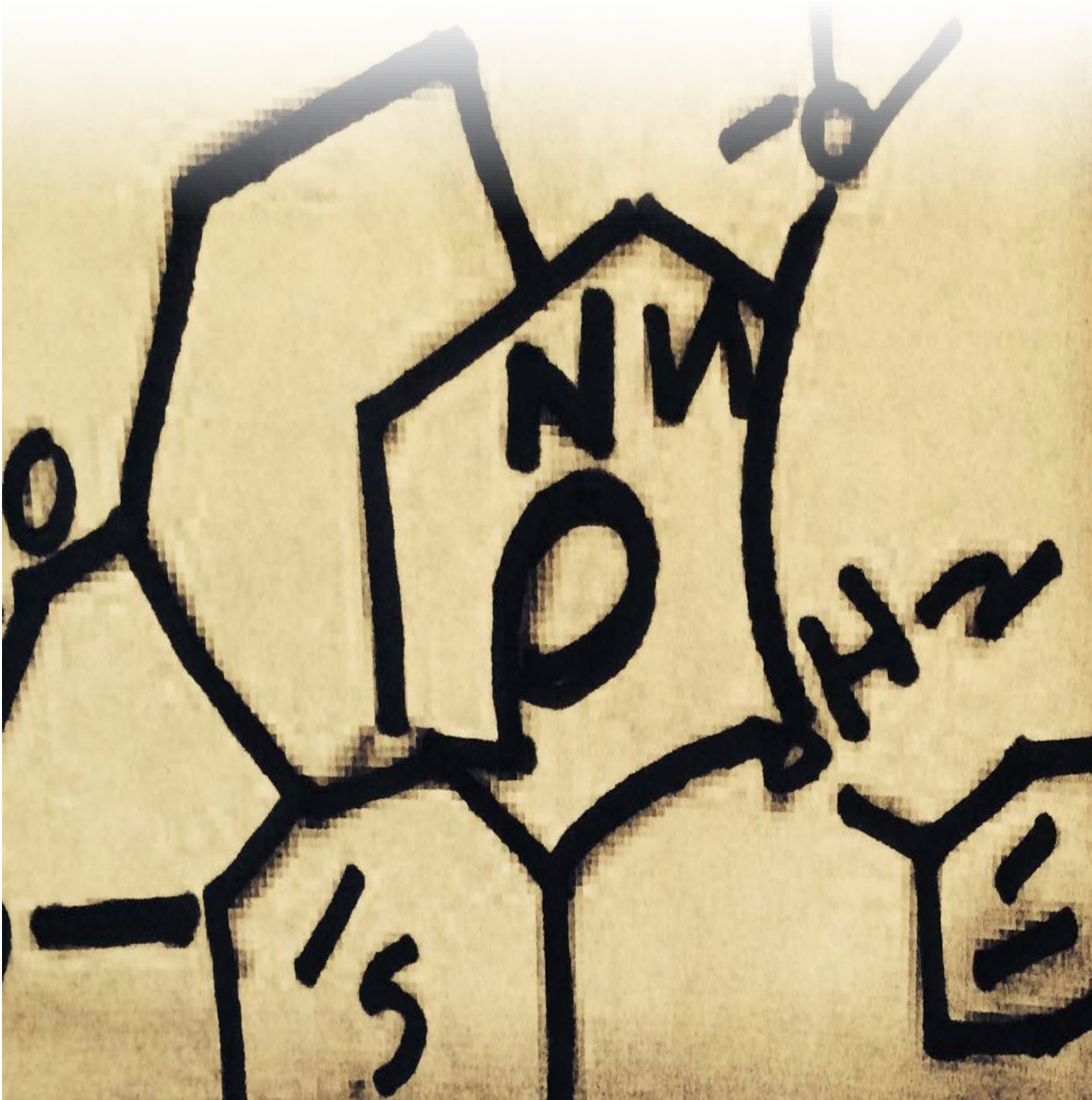
VANDERBILT UNIVERSITY

CTTC Center for Technology Transfer & Commercialization

Small Molecule Therapeutics Pipeline



Vanderbilt University

Small Molecule Pipeline

Vanderbilt Small Molecule Pipelines

Overview

Vanderbilt University has long been a world leader in pharmacology research, and is ideally positioned to lead drug discovery efforts through expanded partnerships with the pharmaceutical and biotechnology industry. Vanderbilt possesses the major infrastructure needed for drug discovery including high throughput screening (HTS), medicinal chemistry, molecular pharmacology, drug metabolism and pharmacokinetics (DMPK), *in vivo*/behavioral capabilities, and an extensive early through late phase human testing environment.

Vanderbilt's drug discovery assets have been centers for both the NIHs Molecular Libraries Probe Production Network and Molecular Libraries Screening Centers Network. Vanderbilt has contributed more than 32 probes through those NIH programs, many of which continued into full drug discovery programs at Vanderbilt and other institutions. Their leadership in helping to deliver tool compounds to the research community which has helped further define the utility of drug targets.

Vanderbilt Institute for Chemical Biology

Augmenting the focused drug development programs described below is an array of core capabilities that Vanderbilt has invested in and developed over the past decade. The Vanderbilt Institute for Chemical Biology (VICB) and Molecular Libraries Probe Production Centers have utilized their high throughput screening facility (HTS) and medicinal chemistry capabilities to generate exciting hits for a variety of indications, and boasts an ever expanding compound library containing more than 300,000 compounds. In addition to providing assay development, medicinal chemistry, HTS screening services, and DMPK assays to Vanderbilt drug discovery research groups, VICB provides access to an array of industry-trained experts. Dr. Dave Weaver, formerly of Bristol Myers Squibb, has pioneered new assays and new fluorescent dyes for use in high throughput screens, as well as new imaging plate readers and analysis software systems.

The high throughput screening core performs at least eight new large screens per year within the HTS facility, as well as smaller screens, continued support for development of ongoing programs (including screening for SAR), as well as assisting with infectious disease screens which are performed offsite but with the Vanderbilt compound collection. Beyond the HTS core, there is also a Chemical Synthesis core, which can assist in SAR and other synthetic chemistry support once a project has graduated from the high throughput screen.

Vanderbilt Center for Neuroscience Drug Discovery

The Vanderbilt Center for Neuroscience Drug Discovery (VCNDD) was the first "industry-like" drug-discovery platform program pioneered by Vanderbilt which focused on a certain set of diseases. Formed in 2003 and led by Drs. Jeffrey Conn and Craig Lindsley, who co-led neuroscience drug discovery efforts at Merck, this center now employs more than 60 full-time faculty and staff specialized in a range of bioscience arenas, including medicinal chemistry, molecular pharmacology, DMPK, and in vivo/behavioral, and have represented backgrounds from more than thirteen pharmaceutical companies.

Since its inception, the VCNDD has secured a total of $85 million in external research funding from industrial, foundation and federal funding sources. This program's impact is evidenced by its success in partnering with four major

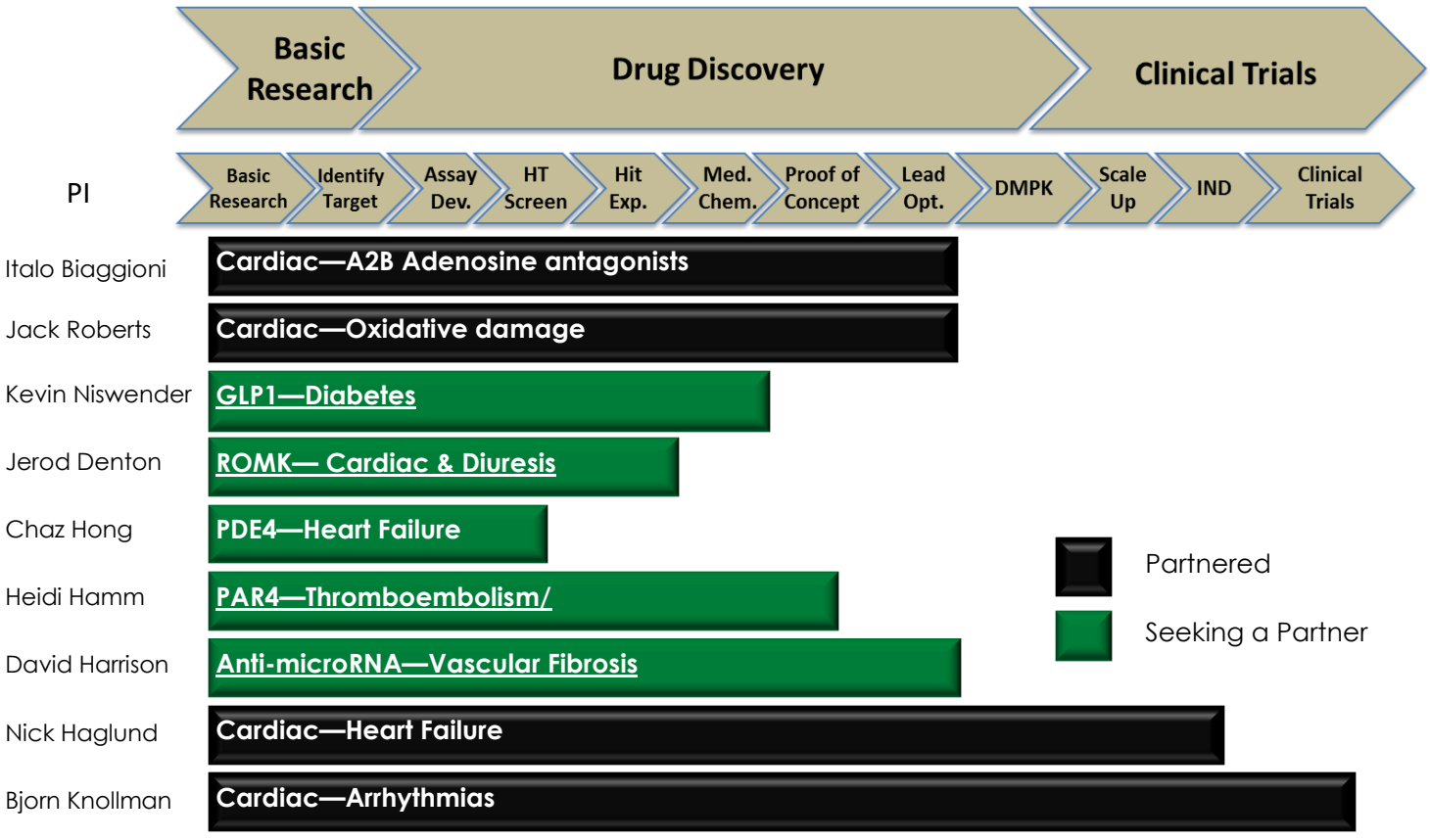
pharmaceutical companies and several biopharma companies to develop new drugs for treating schizophrenia, depression, Parkinson's disease, autism, and Alzheimer's disease. These programs have led to new innovations resulting in six commercial licenses with biotechnology and pharmaceutical companies.

Fragment-based Drug Discovery for Cancer Therapeutics

In 2009, Vanderbilt recruited Dr. Stephen Fesik, divisional VP for Cancer Research at Abbott Laboratories, to lead a new cancer drug development effort with goals analogous to those of our already successful program in the neurosciences. In his short time here, Dr. Fesik has grown his research endeavor to more than 28 full time faculty and staff, employing a fragment-based approach to identify novel, potent cancer therapeutics. He has already been awarded a Pioneer Award from the National Institutes of Health for $2.5 million to support his cancer drug discovery efforts and has entered into three partnerships with outside pharmaceutical companies.

The following pages provide a brief outline of the Vanderbilt small molecule pipeline.

Cardiac and Metabolic



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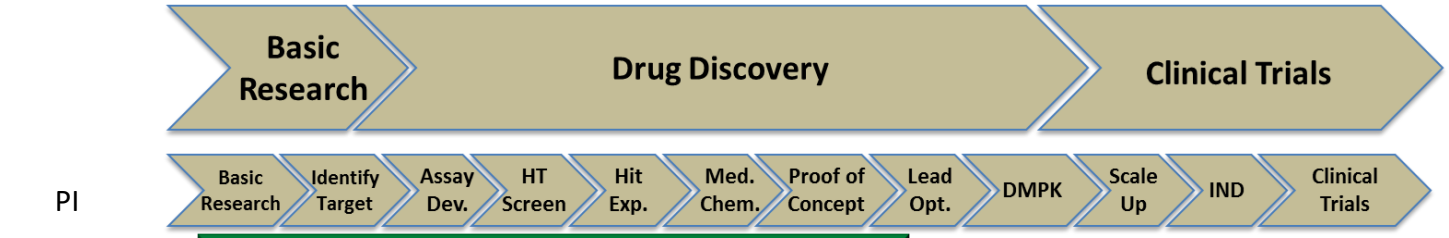
Neuroscience



PI	
VCNDD	mGlu5 PAMs—Schizophrenia
VCNDD	M4 PAMs—Schizophrenia/Alzheimer's
VCNDD	mGlu4 PAMs—Parkinson's Disease
VCNDD	mGlu5 NAMs— L-DOPA induced Dyskinesia in Parkinson's Disease
VCNDD	M1 PAMS—Schizophrenia/Alzheimer's
VCNDD	mGlu3 NAMs—Anxiety, Depressive Disorders
VCNDD	mGlu1 NAMs—Depression
VCNDD	mGlu1 PAMs—Schizophrenia
VCNDD	mGlu2 NAMs—Anxiety, Depressive Disorders
VCNDD	M1 Antagonist—Dystonia
VCNDD	M5 NAMs—Addictive Disorders
VCNDD	M5 PAMs—ADHD
VCNDD	M4 Antagonist—Parkinson's Disease
VCNDD	mGlu3 PAMs—Schizophrenia
Dave Weaver	GIRK—Anxiolytic
Katty Kang	Natural Product—Epilepsy
James Blair	Delirium
Joseph Parello	Collybolide derivative for pain, depression, addiction

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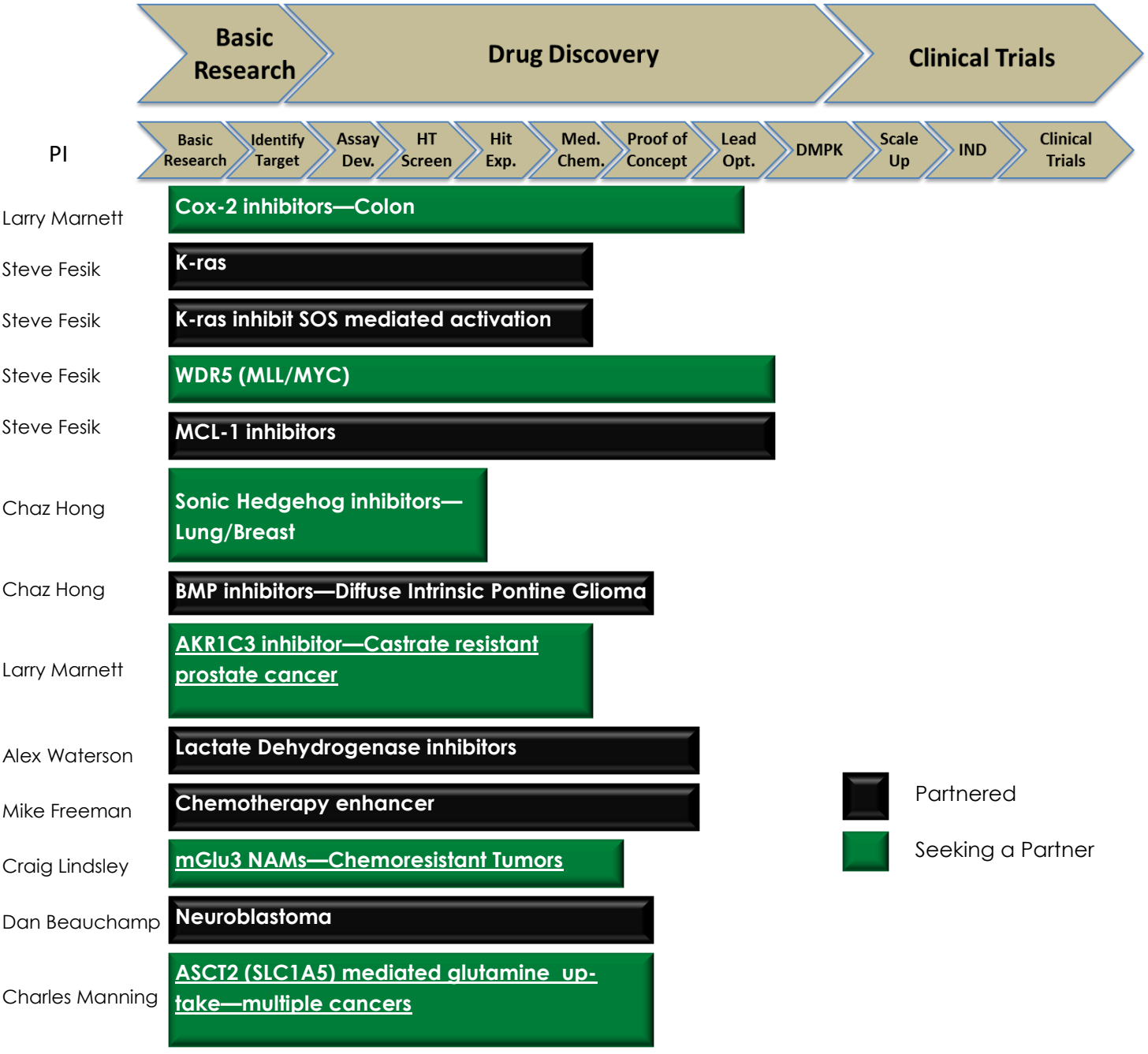
Oncology


Basic Research
Drug Discovery
Clinical Trials
PI
Basic Research
Identify Target
Assay Dev.
HT Screen
Hit Exp.
Med. Chem.
Proof of Concept
Lead Opt.
DMPK
Scale Up
IND
Clinical Trials
Larry Marnett
Cox-2 inhibitors—Colon
Steve Fesik
K-ras
Steve Fesik
K-ras inhibit SOS mediated activation
Steve Fesik
WDR5 (MLL/MYC)
Steve Fesik
MCL-1 inhibitors
Chaz Hong
Sonic Hedgehog inhibitors—Lung/Breast
Chaz Hong
BMP inhibitors—Diffuse Intrinsic Pontine Glioma
Larry Marnett
AKR1C3 inhibitor—Castrate resistant prostate cancer
Alex Waterson
Lactate Dehydrogenase inhibitors
Mike Freeman
Chemotherapy enhancer
Craig Lindsley
mGlu3 NAMs—Chemoresistant Tumors
Dan Beauchamp
Neuroblastoma
Charles Manning
ASCT2 (SLC1A5) mediated glutamine up-take—multiple cancers
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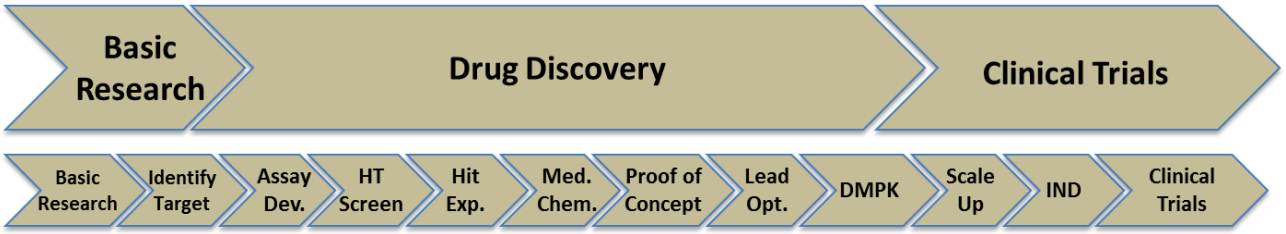
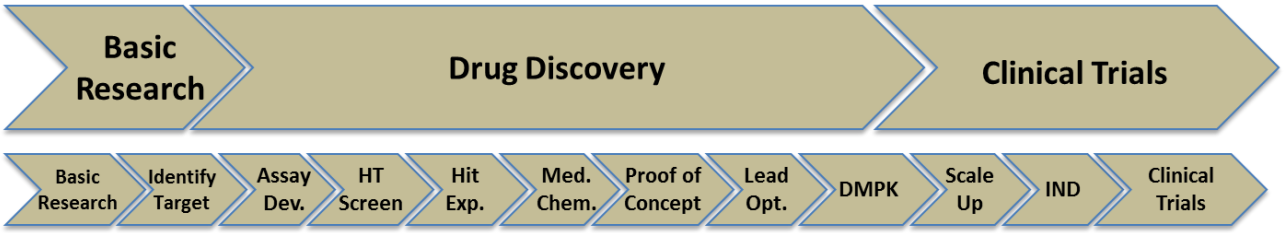
Infectious Disease



PI	
Eric Skaar	Gram + bacteria—See below**
Chris Aiken	HIV— Capsid targeting
Brian Bachmann	Antibiotics — Gram -, Gram + and broad spectrum available

** MRSA, anthrax, bone infection in Cystic Fibrosis, skin infections

Rare/Orphan Diseases



PI	
Chaz Hong	BMP inhibitors—FOP
Steve Fesik	MCL-1—Pancreatic Cancer
Oliver Mcdonald	Metastatic Pancreatic Cancer
Colleen Niswender	mGlu7—Rett Syndrome
VCNDD	M1 PAMs—Rett Syndrome

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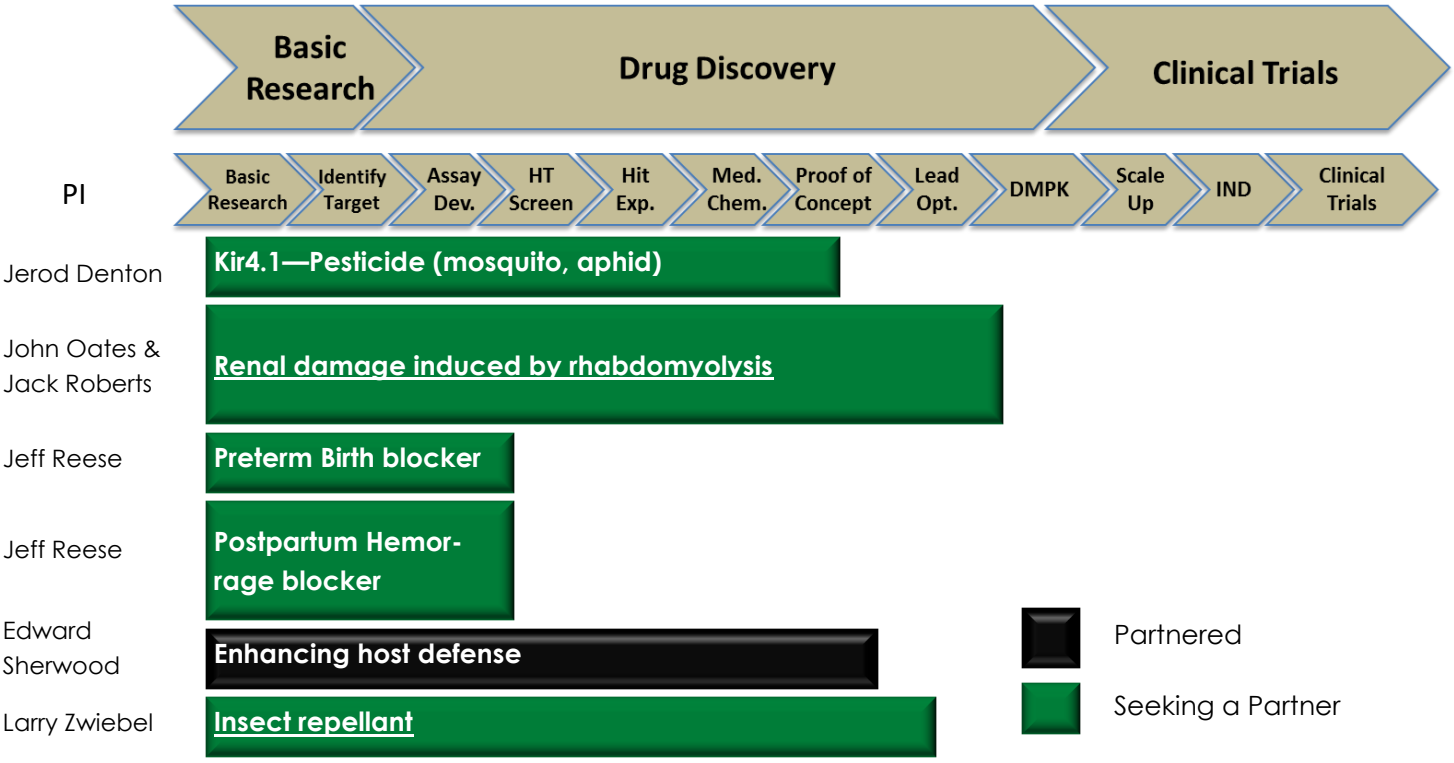
Other Small Molecule Programs



Translational Science and Clinical Trials

As Vanderbilt's drug discovery scientists create novel compositions with the potential of becoming first-in-class therapeutics, they can easily partner with disease specialists and world class leading clinical physicians. Such partnerships early in the process can help design more effective and efficient clinical trials for novel therapeutics. These partnerships are further progressed through teaming with the various cores to assist in the development of companion diagnostics and target validation through other institutional initiatives such as personalized medicine.

In 2007 Vanderbilt University received a $40 million Clinical and Translational Science Award (CTSA) grant, the largest single government research grant in Vanderbilt's history, to expedite the translation of laboratory discoveries to patients in the community. This NIH grant helps fund the Vanderbilt Institute for Clinical and Translational Research (VICTR), which supports the translation of fundamental scientific discoveries into clinical practice and brings basic and clinical researchers together. Additionally, the CTSA program supports the pilot grants, resources and the biostatistics and informatics that are essential for translating new findings into health care applications. Based on the success of the Vanderbilt-run CTSA program, the NIH awarded Vanderbilt a renewal of $46 million in 2011.

In 2011 Vanderbilt was awarded a $20 million grant to be the Coordinating Center for the CTSA consortium, which now includes 60 institutions in 30 states and the District of Columbia. Being named the Coordinating Center further validates the resources and

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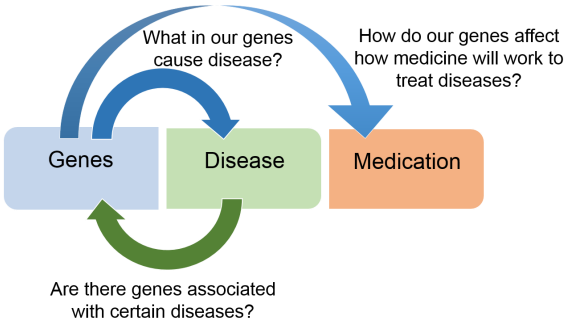
know-how which Vanderbilt has been committed to and invested in for many years around clinical and translation research.



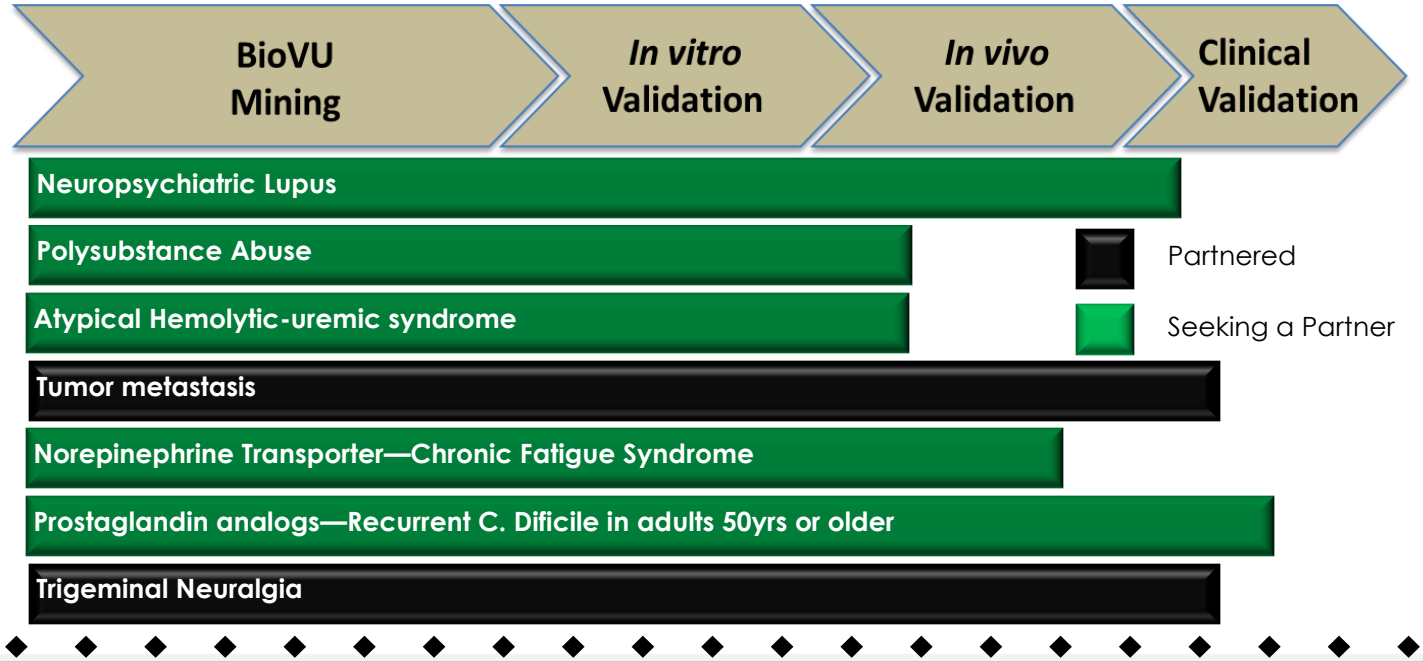
BioVU - DNA Biorepository

For eight years, Vanderbilt has been building a biorepository of DNA extracted from discarded blood collected during routine clinical testing and linked to de-identified medical records in the Synthetic Derivative. BioVU provides enabling resources for exploration of the relationships among genetic variation, disease susceptibility, and variable drug responses, and represents a key first step in moving the emerging sciences of genomics and pharmacogenomics from research tools to clinical practice. A major goal of the resource is to generate datasets that incorporate de-identified information derived from medical records and genotype information to identify factors that affect disease susceptibility, disease progression, and/or drug response. About **500 samples are collected per week** totaling more than **225,000 DNA samples in 2016** in BioVU.

ADDRI - Drug Repurposing

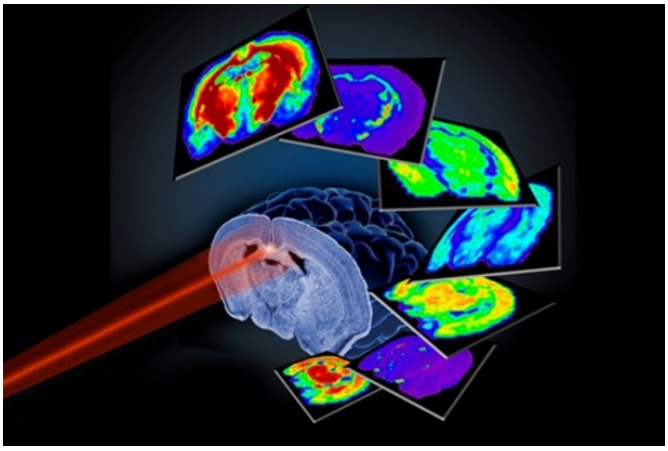
The goal of the Accelerating Drug Discovery and Repurposing Incubator (ADDRI) is to discover new uses for FDA-approved drugs based on an understanding of diseases driven by human genetics. Many people suffer from rare and/or complex diseases with no known treatment options. Despite an understanding of the molecular basis of almost six thousand diseases, we only have about 500 approved therapies. This novel repurposing analysis starts by identifying potential genetic variants of interest based on Phenome Wide Association Studies (PheWAS) performed using de-identified medical records link to BioVU DNA samples. If there are approved drugs that target a specific protein of interest, we leverage the PheWAS results to discover novel gene-disease associations. The team then executes in-depth evidence reviews to determine the plausibility and viability of novel drug-indication pairs. The final step in project initiation is to design experimental approaches to validate new indications. ADDRI has yielded many new uses for approved drugs, some of which are listed below.

Repurposed Drugs



Contact: Center for Technology Transfer and Commercialization 615.343.2430 cttc@Vanderbilt.edu

Imaging



Vanderbilt has an outstanding multi-faceted imaging facility, the Vanderbilt University Institute of Imaging Science (VUIIS), currently located in a new building that boasts four floors and 35,000 sq.ft. Within the institute are the Center for Human Imaging and the Center for Small Animal Imaging (CSAI). Both are equipped with an array of imaging resources including positron emission tomography, Varian MRI scanners, high-frequency ultrasound, single-photon emission computed tomography, x-ray, and bioluminescence/fluorescence imaging systems. The CSAI also houses an animal surgery suite, which consists of two fully equipped surgical benches with anesthesia equipment, surgical microscopes, stereotaxic frames, water-circulating heating pads, a blood gas analyzer, and a biosafety low flow hood for injections and perfusions. Additionally, the radiopharmacology and radiochemistry division is equipped for radiochemical operations with ^{18}F, ^{11}C, ^{123}I and other radionuclides. The recently renovated laboratory includes separate areas for research and radiopharmaceutical production. A cyclotron in the PET facility is capable of producing ^{18}F, ^{11}C, ^{13}N and ^{15}O.

PI	Basic Research	Target Selection and Validation	Identification of Markers	Animal Studies	Analytical Validation	Clinical Validation
Larry Marnett	Head/neck and colon cancer imaging—Cox-2 binding agents					
Larry Marnett	Hypoxia sensitive agents for solid tumor imaging					
Wellington Pham	Cox-2 binding agents for cancer imaging					
Charles Manning	TPSO ligands for imaging of solid tumors					
Charles Manning	Cannabinoid 2 receptor for cancer or neurodegenerative disease imaging					
Charles Manning	Cyclen-based chelates for imaging cancer					
Charles Manning	Peripheral benzodiazepine receptor ligands for imaging cancer					
John Penn	Retinal Imaging					
Charles Manning	PET tracers for multiple cancers (ASCT2)					

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For further information, please contact us:

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