



Yale/NIDA Neuroproteomics Center

External Advisory Board Meeting

May 1, 2019

Paul Greengard (1925-2019)

- Awarded 2000 Nobel Prize in Physiology or Medicine for his research on neurochemical signaling in the brain.
- Investigator Nestler: *“Paul Greengard was a paradigm-shifting scientist who changed fundamentally the way we understand cell signaling. He was uniquely generous and was like a second father to so many of us. An end of an era. He will be missed”*.



Program Outline

- **Brief overview of Center**
- **Core technologies and biotechnology research presented by Core Directors and staff**
- **Progress of established research projects presented by seven Center investigators**
- **Progress of Pilot Project grants presented by four awardees**
- **Closing summary by PI Angus Nairn**
- **External Advisory Board Meeting with Angus Nairn and Ken Williams**
- **In total there will be 17 presentations with morning and afternoon coffee breaks and lunch around noon**
- **Each talk will be 15 min followed by 5 min for questions**

Overall Goal: Seek advice from EAB on how best to improve the Center and to submit the strongest possible competing grant renewal this Fall.

Yale/NIDA Neuroproteomics Center

- **PI/Co-Director Angus Nairn**
 - Charles Murphy Professor of Psychiatry and Pharmacology
 - Office in CT Mental Health Center near many Center investigators

- **PI/Co-Director Ken Williams**
 - Founder (1980) Keck Laboratory
 - Professor (Adjunct) Research, Mol. Biophysics & Biochemistry
 - Office is at 300 George St, houses many of the Center's Cores and Keck Lab
 - Collaborated with Angus since their 1989 JBC publication on DARPP32

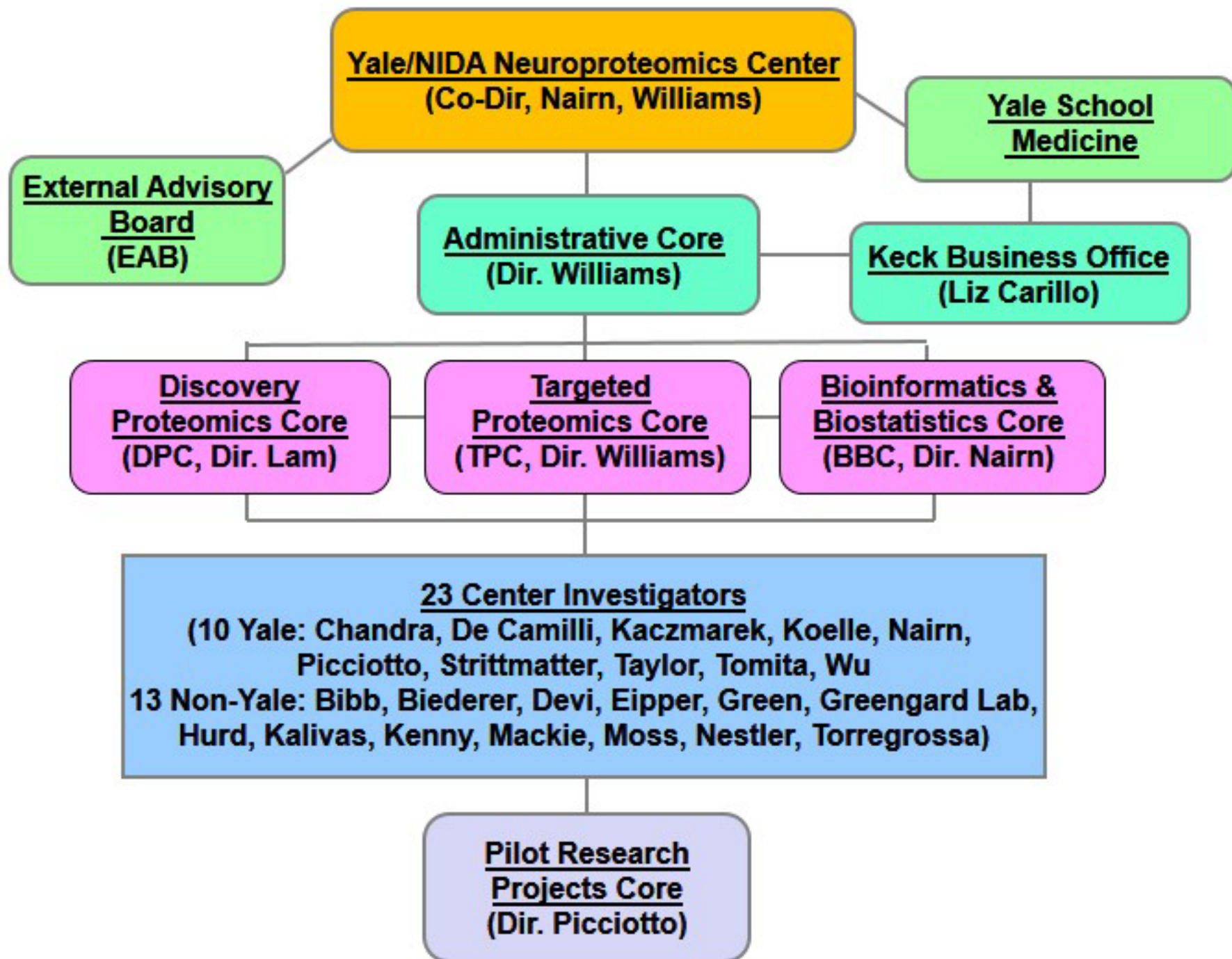
- **Theme of the Center is: “Proteomics of Altered Signaling in Drug Addiction”**

- **Center has 9 Key Personnel and 23 Investigators at 10 Institutions**

- **Grant Funding:**
 - Center has been in existence for ~15 years, it was established 8/23/2004 with P30 Center Grant DA018343
 - Competing renewals were awarded in 2009 and 2015
 - Grant Year 14 funding (6/18 - 5/19) is \$928K (DC)
 - Grant funds 90% of cost of providing core technologies to center investigators, biotechnology research, Pilot Project grants, and administration.

Yale/NIDA Neuroproteomics Center Has Five Cores

Core	Key Personnel	Dept.	Role
Administrative	Angus Nairn	Psychiatry	PI, Co-Director
	Ken Williams	Mol. Biophys. Biochem.	
Bioinformatics & Biostatistics (BBC)	Angus Nairn	Psychiatry	Director
	Rob Bjornson	Computer Science	HPC
	Mark Gerstein	Mol. Biophys. Biochem.	Bioinformatics
	Hongyu Zhao	Biostatistics	Biostatistics
Discovery Proteomics	TuKiet Lam	Mol. Biophys. Biochem.	Director
	Pietro DeCamilli	Cell Biology	Phosphoinositides Analyses
	Ewa Folta-Stogniew	Mol. Biophys. Biochem.	Biophysics
Targeted Proteomics	Ken Williams	Mol. Biophys. Biochem.	Director
Pilot Projects	Marina Picciotto	Psychiatry	Director



Yale/NIDA Neuroproteomics Center Mission Statement & Goals

- **The Center brings 23 neuroscientists from 10 institutions together in a unique synergy with the Keck Lab to use cutting edge technologies to identify adaptive changes in neuronal signaling that occur in response to drugs of abuse.**
- **Discovery Proteomics Core (DPC) optimizes existing and develops new technologies to reach deeper into the neural proteome. Biophysical technologies extend proteome analyses into the functional domain while phosphoinositide analyses provide an increasingly biological systems level approach to understanding novel aspects of neuronal signaling and the actions of drugs of abuse.**
- **Targeted Proteomics Core carries out analyses that enable relative and absolute quantitation of targeted protein levels or alterations in their PTMs to validate differential changes in expression uncovered by protein profiling analyses carried out in the DPC.**
- **Bioinformatics and Biostatistics Core (BBC) provides essential support that positively leverages the value of the proteomic technology cores. A major initiative is to develop novel methods for deep integration of genomic, transcriptomic, and proteomic data with brain region and cell type-specificity.**
- **Pilot Research Project Core is a cornerstone in our efforts to encourage strong mentoring relationships that will help attract and train future outstanding neuroscientists in proteomic approaches and cell signaling.**

Synergies Between the Yale/NIDA Neuroproteomics Center and the Keck Lab

- **8 mass spectrometers including Fusion, Q Exactive Plus, and HF-X purchased by Keck (with support from NIH and YSM) since 2007 for >\$5 million are available to support the Discovery and Targeted Proteomics Cores.**
- **Discovery and much of the Targeted Proteomics Core is located within 7,500 ft² in the Keck MS & Proteomics Resource.**
- **The Center's Biophysics and Biostatistics Core Sections are located within the corresponding Keck Resources.**
- **Keck Genomic Resources provide complementary technologies that are not available through the Center.**
- **Improved technologies developed in the Keck Lab are made available to the Center and new technologies such as the PSD DIA and PRM assays developed in the Center are positively leveraged by their availability to users of the Keck Lab.**
- **The Center strongly supports the SIG applications submitted by the Keck MS & Proteomics Resource.**
- **Investigators and Pilot Project Grant awardees in the Center help provide a stable user base for the Keck MS & Proteomics Resource.**

Yale/NIDA Neuroproteomics Center External Advisory Board (EAB)

(Highlight = 5 Members of 2004 EAB, *5 Attendees of 2019 EAB Meeting)

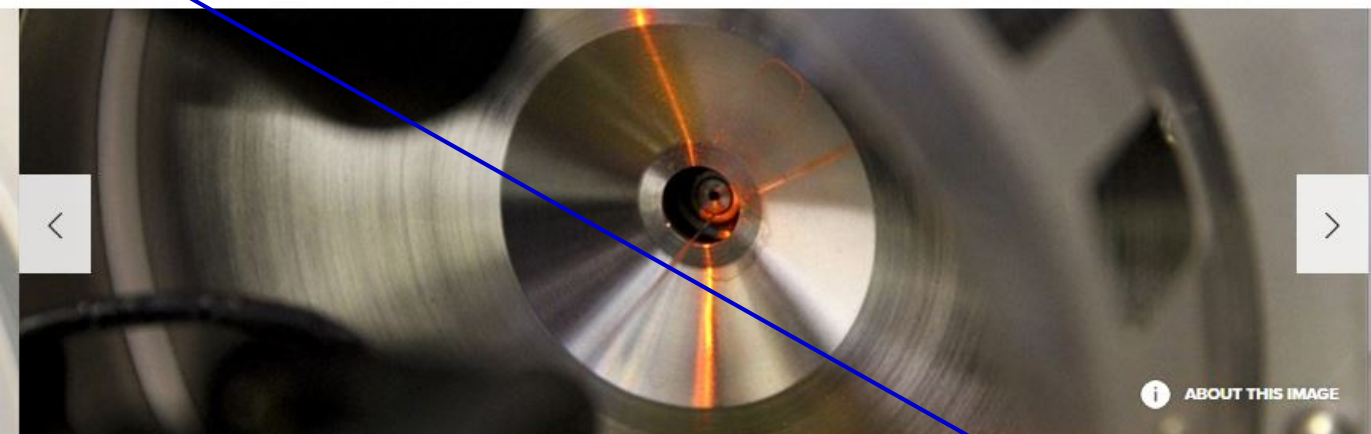
	Name	Department	Institution
1	Dr. Brian Chait*	Camille & Henry Davis Prof., Laboratory of Mass Spectrometry	Rockefeller U.
2	Dr. Edward Hawrot*	Senior Assoc. Dean, Biology Program; Prof. Med. Sci.	Warren Alpert Medical School at Brown U.
3	Dr. Peter McPherson	James McGill Prof., Neurology & Neurosurgery, Anatomy & Cell Biology	Montreal Neurological Institute
4	Dr. David Muddiman*	Distinguished Prof. Chemistry; Dir. Mol. Education, Technology & Research Innovation Center	North Carolina State U.
5	Dr. Andrey Rzhetsky*	Prof. Human Genetics	University Chicago
6	Dr. Paul Tempst*	Prof. Molecular Biology	Memorial Sloane Kettering Cancer C.
7	Dr. Marina Wolf	Prof. Behavioral Neuroscience	Oregon Health & Science U.

Yale/NIDA Neuroproteomics Center

Projects Cores Publications - Technologies Database Meetings Pilot Projects - About Us -

Total Requests:
8,499/Year

Most Requested Page is Front Page: 3,300 Views /Year



Yale/NIDA Neuroproteomics Center

The Yale/NIDA Neuroproteomics Center, which was founded 8/23/2004 (DA018343), brings exceptionally strong Yale programs in proteomics and signal transduction in the brain together with neuroscientists from nine other institutions across the U.S. to identify adaptive changes in protein signaling that occur in response to substances of abuse.

The main goal of the Center, whose theme is "Proteomics of Altered Signaling in Addiction", is to use cutting edge proteomic technologies to analyze neuronal signal transduction mechanisms and the adaptive changes in these processes that occur in response to drugs of abuse.

Twenty-three faculty with established records of highly innovative research into the molecular actions of psychoactive addictive drugs, as well as of other basic aspects of neurobiology, are working together in a unique synergy with the Keck Foundation Biotechnology Resource Laboratory to continually strengthen the Yale/NIDA Neuroproteomics Center.

With Co-Directors Drs. Angus Nairn (Psychiatry) and Kenneth Williams (Mol. Biophys. & Biochem.) in the Administration Core, the Center includes Discovery Proteomics (DPC) and Targeted Proteomics (TPC) technology cores. Biophysical technologies from the DPC extend protein profiling analyses into the functional domain while lipid analyses from the DPC very positively leverage proteome level analyses to provide an increasingly biological systems level approach. A Bioinformatics and Biostatistics Core, which includes high performance computing and the Yale Protein Expression Database (YPED), provides essential support that positively leverages the value of each of the proteomic technology cores.

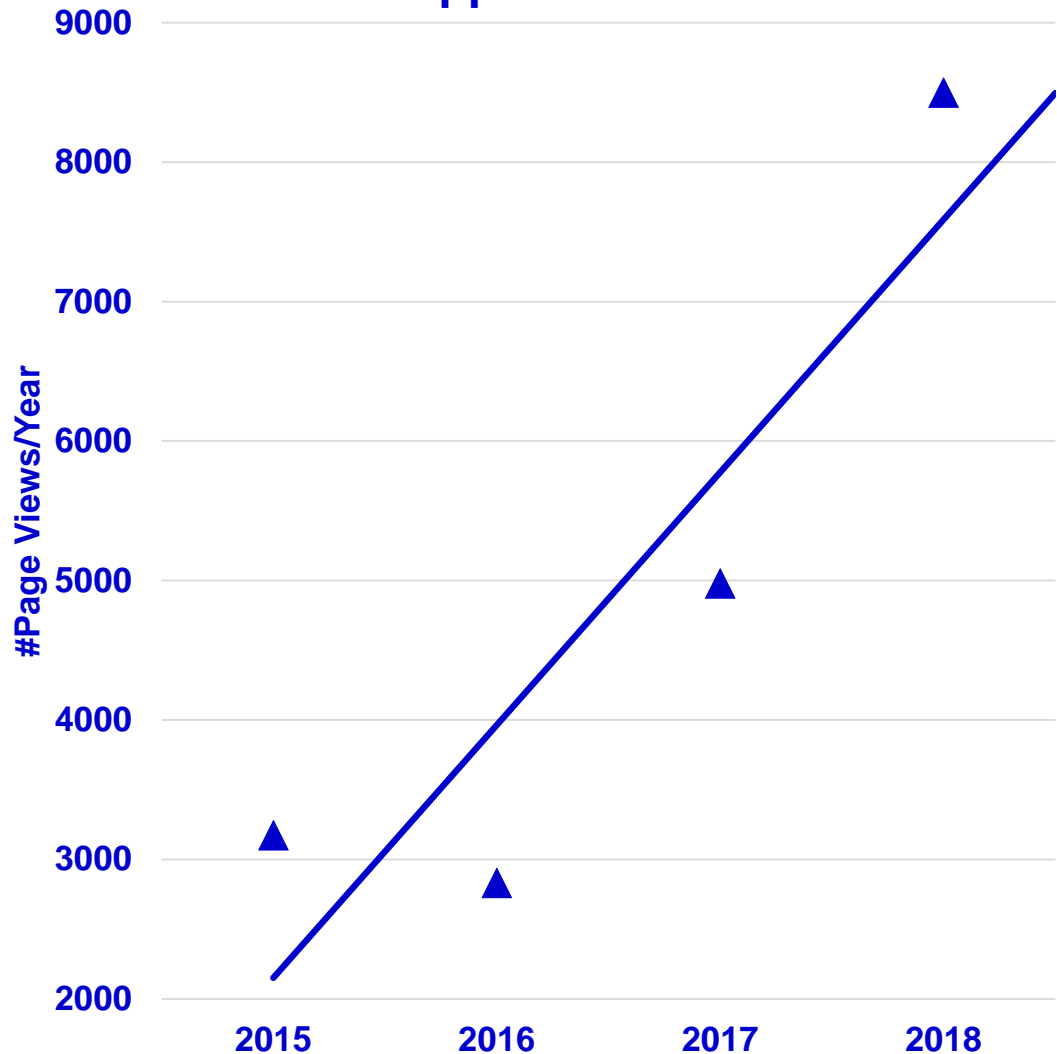
IMPORTANT NOTICES AND INFORMATION

- [Yale/NIDA Neuroproteomics Center Twitter Page](#)
- [Pilot Research Project Grants](#)
- [Publications](#)
- [Proteomes Journal Special Issue "Neuroproteomics"](#)
- [Posters](#)
- [Newsletters](#)
- [Research in Progress Meetings](#)
- [ProteomicsBrowser Tool](#)
- [Proteome Software Scaffold](#)
- [Education](#)

Second Most Requested Page is Projects: 745 Views/Year

<https://medicine.yale.edu/keck/nida/index.aspx>

3-Fold Increase in Page Views of Center Web Pages Since Renewal of the Center's Last Competing Grant Application



2018 Stats

8499 Page Views/Year
~23 Page Views/day
by
997 Users from 51
Countries

Selected Center Accomplishments Since Submission of Last Competing Renewal on 9/25/14

➤ Publications

- 66 Publications
- One manuscript under revision and two submitted manuscripts.

➤ Instrumentation

- 3 new mass spectrometers including Orbitrap Fusion, Q Exactive Plus, and Q Exactive HF-X installed in Keck Lab since 2015.
- Pending Yale request from Keck Lab for a Bruker Trapped Ion Mobility Spectrometry (tims)TOF instrument to provide increased depth of protein and PTM coverage.

➤ Pilot Project Grants

- 19 Pilot Project Grants awarded in Grant Years 11-14.

➤ New Technologies

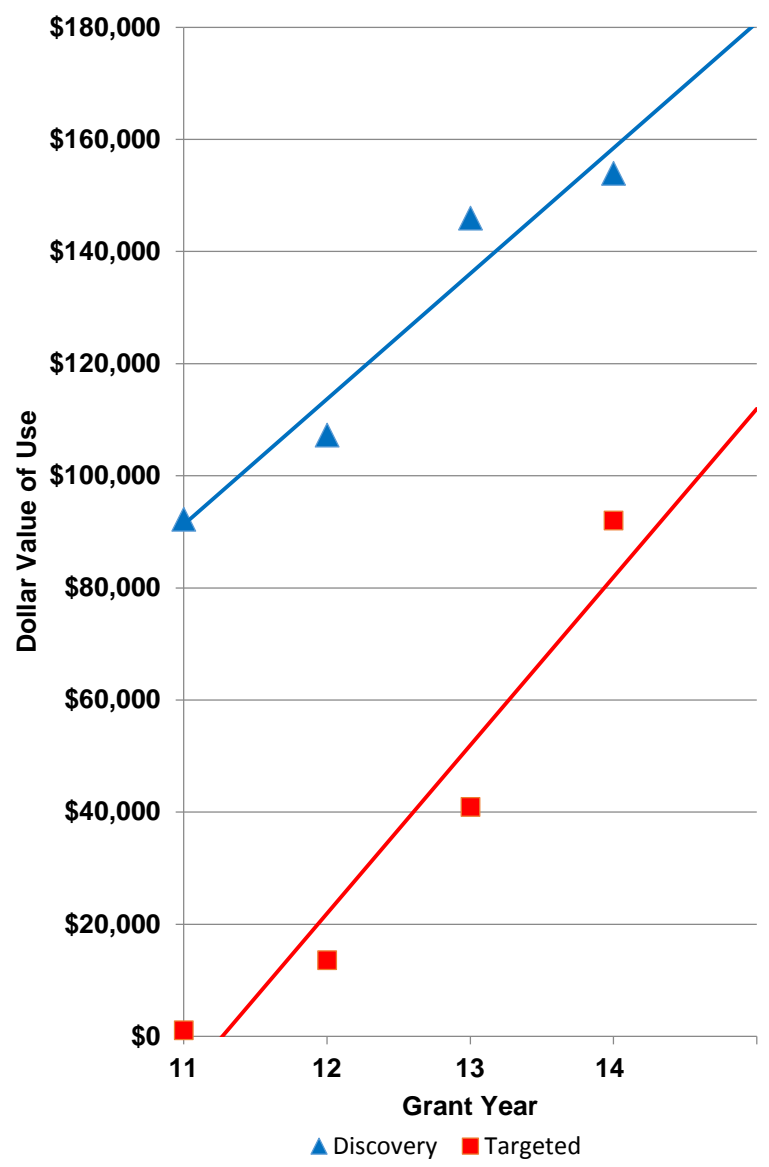
- MRM assay for 112 rat brain synaptic proteins (Colangelo et al, 2015).
- PRM assay for 50 rat/mouse PSD proteins (Wilson et al, 2019)
- DIA assay for 2,134 rat/mouse PSD proteins (Wilson et al, 2019)

➤ Special Issue of Journal *Proteomes* on Neuroproteomics Co-Edited by the PIs

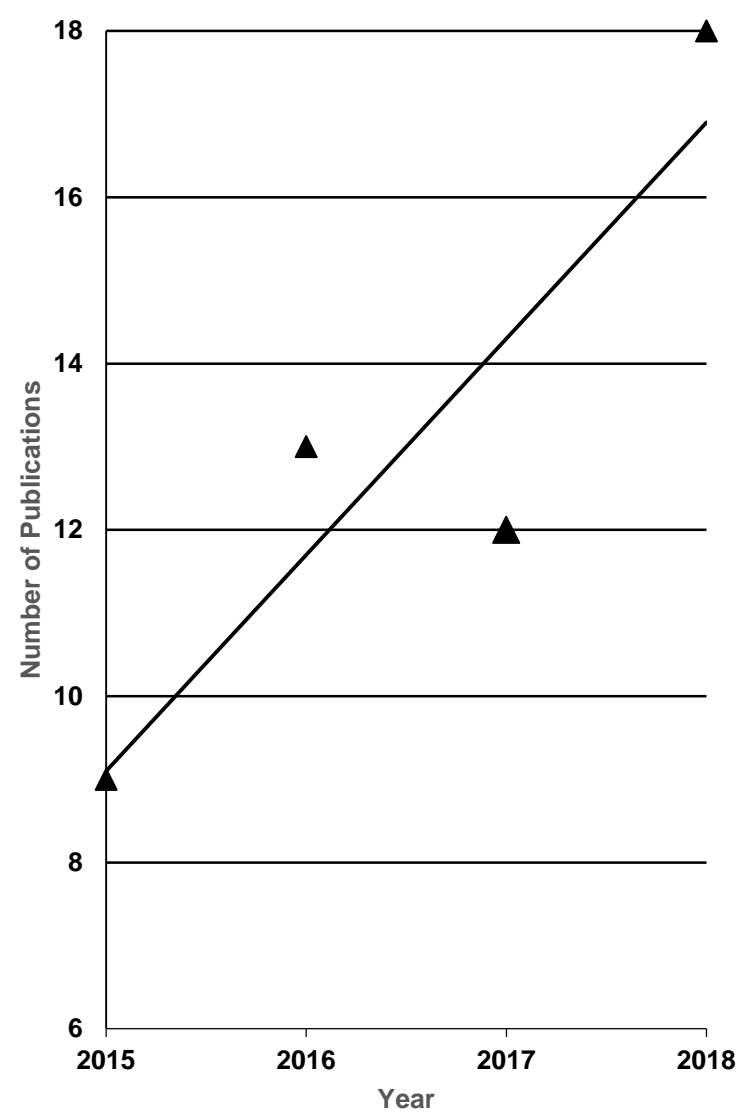
- 16 publications including 8 by the Center and 8 by other authors including Anthony Baucum, Seth Grant, Jeffrey Savas, John Yates, and others.

2.6 Fold Increase in Annual Use of MS/Proteomics Technologies Parallels a 2 Fold Increase in Annual Publications Over Last Four Years

Use of MS/Proteomics Technologies



Annual Publications



Yale/NIDA Neuroproteomics Center Year 14 Pilot Project Grants

PI	PI Rank	University	Mentor	Title
Caleb Browne	Postdoct.	Mt Sinai Med. School	Eric Nestler	Proteomic profiling of NAc synaptosomes during early and extended withdrawal from self-administered cocaine
Ayanabha Chakraborti	Senior Res. Assoc.	U. Alabama	James Bibb	Profiling the Nucleus Accumbens proteome in an experimental model of inflammatory bowel disease
Tina Franklin	Postdoct.	Yale U.	Ron Duman	Stress-induced dysregulation in microglial HMGB1 signaling
Stephanie Groman	Assoc. Res. Sci.	Yale U.	Jane Taylor	A 'targeted' approach to identify the proteins underlying the biobehavioral mechanisms of addiction
Angela Lee	MD/Ph.D. Student	Yale U.	Marina Picciotto	Sex differences in nicotine-induced changes of the mouse brain proteome

**Yale/NIDA Neuroproteomics Center-Supported Contributors to the Special Issue
of the Journal *Proteomes* on Neuroproteomics
Co-Editors: A. Nairn & K. Williams**

#	Senior Author	Title	Institution
1	Mary Torregrossa	Phosphoproteomic Analysis of the Amygdala Response to Adolescent Glucocorticoid Exposure Reveals G-protein Coupled Receptor Kinase 2 (GRK2) as a Target for Reducing Motivation for Alcohol	U. Pittsburgh
2	Thomas Biederer	Mapping the Proteome of the Synaptic Cleft Through Proximity Labeling Reveals New Cleft Proteins	Tufts U.
3	Elizabeth Eipper	Proteases Shape the Chlamydomonas Secretome: Comparison to Classical Neuropeptide Processing Machinery	UCONN Health Center
4	Drew Kiraly	Granulocyte-colony Stimulating Factor Alters the Proteomic Landscape of the Ventral Tegmental Area	Mount Sinai School of Medicine
5	Marina Picciotto	Evaluation of the Phosphoproteome of Mouse Alpha 4/Beta 2 Containing Nicotinic Acetylcholine Receptors In Vitro and In Vivo.	Yale U.
6	Junmin Park	Phosphorylation of the AMPAR-TARP Complex in Synaptic Plasticity	Wayne State U.
7	Angus Nairn	Cell-type-specific Proteomics: A Neuroscience Perspective	Yale U.
8	Angus Nairn	Development of Targeted Mass Spectrometry-Based Approaches for Quantitation of Proteins Enriched in the Postsynaptic Density (PSD)	Yale U.

Yale/NIDA Neuroproteomics Center Investigators - 2019

Yale University

Sreeganga Chandra

Pietro DeCamilli

Len Kaczmarek

Michael Koelle

Angus Nairn*

Marina Picciotto*

Stephen Strittmatter

Jane Taylor*

Susumo Tomita

Dan Wu

Mt. Sinai School of Medicine

Lakshmi Devi*

Yasmin Hurd*

Paul Kenny*

Eric Nestler*

Tufts U.

Thomas Biederer*

Steven Moss

Indiana U., MUSC, Rockefeller U., U. Ala., U. Chicago, U. Conn., U. Pitts.

James Bibb

Elizabeth Eipper

William Green*

Paul Greengard Lab

Peter Kalivas*

Ken Mackie*

Mary Torregrossa*

2004 investigators

***12 of 23 Center Investigators
Have NIDA Research Grant
Support**

Proteomics of Altered Signaling in Drug Addiction



Pre- and Post-Synaptic Signaling

Transcriptional Regulation

Endocytosis and Exocytosis

Regulation of the Cytoskeleton

Neuronal Development

Neuronal Plasticity

Cell Death



MudPIT

LFQ

iTraq

TMT

Phosphoproteome Profiling

DIA

PRM



Identification and Characterization of Signaling Proteins Whose Expression is Altered by Drugs of Abuse

Program

Talk#	Speakers	Institution	Core or Project Title	Start Time	Min
Continental Breakfast – All Attendees Invited				8:40 AM	20
1	Ken Williams & Angus Nairn	Yale U.	Center Overview	9:00 AM	20
2	TuKiet Lam	Yale U.	Protein & PTM Profiling and Identification Core Section	9:20 AM	20
3	Rashaun Wilson	Yale U.	Development of Targeted Mass Spectrometry-based Approaches for Quantitation of Proteins Enriched in the Postsynaptic Density (PSD)	9:40 AM	20
4	Gang Peng	Yale U.	ProteomicsBrowser: MS/Proteomics Data Visualization and Investigation	10:00 AM	20
Morning Coffee Break				10:20 AM	20
5	Ewa Folta-Stogniew	Yale U.	Biophysics Core Section	10:40 AM	20
6	Mark Gerstein & Prashant Emani	Yale U.	Isoform Level Interpretation of High-throughput Proteomic Data Enabled by Deep Integration with RNA-seq	11:00 AM	20
7	Pietro DeCamilli	Yale U.	Lipid Transport at Membrane Contact Sites	11:20 AM	20
8	Thomas Biederer	Tufts U.	Mapping the Proteome of the Synaptic Cleft Through Proximity Labeling Reveals New Cleft Proteins	11:40 AM	20
Buffet Lunch – All Attendees Welcome				12:00 PM	40
9	Stephanie Groman (Taylor)	Yale U.	A ‘Targeted’ Approach to Identify the Proteins Underlying the Biobehavioral Mechanisms of Addiction	12:40 PM	20
10	Mary Torregrossa	U. Pittsburgh	Phosphoproteomic Analysis of Cocaine Memory Extinction and Reconsolidation in the Nucleus Accumbens	1:00 PM	20
11	Betty Eipper	U. Conn.	Brain Region and Isoform-Specific Phosphorylation Alters Kalirin SH2 Domain Interaction Sites and Calpain Sensitivity	1:20 PM	20
12	Drew Kiraly	Mt Sinai Sch. Med.	Granulocyte-colony Stimulating Factor Alters the Proteomic Landscape of the Nucleus Accumbens	1:40 PM	20
Afternoon Coffee Break				2:00 PM	20
13	Michael Koelle	Yale U.	Proteomic Analysis of Complexes Formed by the Neural G Protein G α	2:20 PM	20
14	Sreeganga Chandra	Yale U.	Understanding the impact of disaggregases through unbiased proteomics	2:40 PM	20
15	Marina Picciotto and Angela Lee	Yale U.	Evaluating the Phosphoproteome of Mouse α 4/b2 nAChRs and Effects of Nicotine on the VTA Proteome in Male and Female Mice	3:00 PM	20
16	Becky Carlyle (Nairn)	Harvard Medical School	A Multiregional Proteomic Survey of the Postnatal Human Brain	3:20 AM	20
17	Angus Nairn	Yale U.	Current and Future Challenges in Neuroproteomics	3:40 PM	20
(Closed) External Advisory Committee Meeting with Angus Nairn and Ken Williams				4:00 PM	30