Addiction Science for New Therapies at The Scripps Research Institute
Addiction touches almost all of us in some way. According to a recent survey, one in every 10 Americans is addicted to alcohol or drugs—more than 23 million of us. Yet, only slightly more than 10 percent of those who suffer from the disease of addiction receive medication to treat it. Science can help change this picture.

Understanding the biological, environmental and genetic factors that contribute to addiction is absolutely critical to overcoming this epidemic. The Scripps Research Institute (TSRI) has long been a leader in the field of addiction studies, conducting groundbreaking research that has changed the way we think about addiction and how we go about treating it and saving lives.
A Neglected Crisis

- Alcohol abuse leads to 88,000 deaths in the US each year, according to the Centers for Disease Control (CDC); an estimated 76 million Americans have been exposed to alcoholism in the family.

- Cigarette smoking kills some 440,000 Americans and six million people worldwide every year.

- Use of illicit drugs—including cocaine, methamphetamine, heroin, “bath salts” and other drugs of abuse (including abuse of prescription drugs, such as Oxycontin)—cost the nation an estimated $193 billion due to crime, healthcare and lost productivity.

- Drug overdoses kill nearly 40,000 each year.

- Estimated overall costs of substance abuse for the nation exceed $600 billion annually, according to the National Institute on Drug Abuse.
Addiction Is a Disorder with Biological Roots

- Addictive substances can change brain chemistry.
- With repeated use of an addictive substance, brain circuits can become permanently reset, leading to a skewed perception of reward, motivation and self-control.
- Ceasing the consumption of an addictive substance can lead to withdrawal symptoms from depression, anxiety and sleep disturbances to delirium and life-threatening convulsions.
Despite the great need for research into addictive disorders and new ways to combat them, federal funding for basic biomedical research has been declining in real dollars.

The research funded by the National Institutes of Health (NIH) and the National Science Foundation (NSF) tends to be incremental. What is needed to achieve scientific breakthroughs are high-risk, high-reward endeavors.

Pharmaceutical companies rarely invest in the basic biomedical research necessary to find new approaches to therapies, vaccines and diagnostics.

Still, addiction continues to devastate individuals, families and communities.
The initiative brings together neuroscientists, biologists, chemists and medicinal pharmacologists to collaborate on new approaches to taming addiction.

The center will harness a critical mass of innovative scientists to make the development of groundbreaking treatments against drug abuse a reality.

Together, the scientists at the heart of this initiative will:

- Learn more about how drugs affect brain function.
- Find new therapies to counteract addictive effects.
- Advance these drug candidates and vaccines to clinical trials.
- Ultimately, provide better tools to people with addictive disorders and their physicians to help conquer the problem.
The institute has:

- A track record of basic discoveries translated into new therapies, including treatments for arthritis, lupus, hemophilia and cancer.
- More than 50 companies launched from its discoveries.
- More than 800 patents on innovative technologies.
- 30 pharmaceuticals currently in clinical development.
- Recognition as a leader at the intersection of biology and chemistry—ranked number one in the world in chemistry, number two in microbiology (ranked by Thomson Reuters, citations per paper over a decade).
- Potential synergy with ongoing addiction research, funded by:
  - The Pearson Center for Alcohol and Addiction Research, established with a multi-million dollar gift from Mark Pearson to combine the latest biomedical research with clinical trials.
  - The Alcohol Research Center, supported by the National Institutes of Health (NIH) for the last 25 years to study the effects of alcohol on the brain.
  - A number of other federal grants to develop new treatments for drug addiction.
TSRI Scientists at the Forefront

- TSRI scientists are leaders in the field of addiction research. Their many significant contributions have included:
  - Facilitating the approval of two drugs to treat alcohol dependence, with a faculty member serving as overall principal investigator for the US multicenter study of acamprosate, approved for use in the US in 2004, and conducting seminal work on nalmefene, approved by the European Medicines Agency in 2013.
  - Developing an antidote for cocaine overdose in a pre-clinical study.
  - Creating preliminary vaccines against the effects of nicotine, heroin, cocaine and methamphetamine—potential treatments that could support addicts committed to recovery by preventing these substances from ever reaching the brain.
  - Conducting the first randomized, controlled clinical trial showing that gabapentin, an FDA-approved drug used for seizures and some types of pain, is safe and effective in treating alcohol dependence while diminishing mood and sleep disturbances.
  - Discovering that binge drinking produces more profound changes in the brain than drinking a moderate amount every day.

continued
Showing a combination of two existing medications (naltrexone and buprenorphine) has potential for people addicted to cocaine, offering a therapy that would reduce their craving for the drug and blunt their symptoms of withdrawal.

Finding the illicit drug known as “bath salts” could be more addictive than methamphetamine.

Identifying a pathway in the brain that regulates an individual's vulnerability to the addictive properties of nicotine, suggesting a new target for anti-smoking therapies.
Some of Our Researchers

For faculty bios, see www.scripps.edu

- Thomas Bannister, PhD
- Laura Bohn, PhD
- Candice Contet, PhD
- Cindy Ehlers, PhD
- Ron Davis, PhD
- Brock Grill, PhD
- Donna Gruol, PhD
- Scott Hansen, PhD
- Kim Janda, PhD
- Theodore Kamenecka, PhD
- George Koob, PhD (on leave)
- Jeanne Loring, PhD
- Chitra Mandyam, PhD
- Remi Martin-Fardon, PhD
- Kirill Martemyanov, PhD
- Barbara Mason, PhD
- Mark Mayford, PhD
- Courtney Miller, PhD
- Larry Parsons, PhD
- Marisa Roberto, PhD
- Amanda Roberts, PhD
- Pietro Sanna, MD
- Paul Schweitzer, PhD
- Michael Taffe, PhD
- Sunmee Wee, PhD
- Friedbert Weiss, PhD
- Eric Zorrilla, PhD
Awards and Honors

TSRI faculty in the field of addiction research have been recognized with:

- A Presidential Early Career Award for Scientists and Engineers, the highest honor bestowed by the US government on scientists and engineers in early stages of independent research careers (Roberto).
- Prestigious NIH MERIT awards for addiction research (Mason, Koob, Ehlers, Weiss).
- The Italian Republic’s highest honor “Ordine al Merito della Repubblica Italiana” (Order of Merit or knighthood) for scientific research (Roberto).
- Joseph Cochin Young Investigator Award for outstanding early achievements in the field of drug abuse (Bohn).
- Appointment to direct the National Institute on Alcohol Abuse and Alcoholism of the NIH (Koob, currently on a leave of absence from TSRI to run the agency).
- Honorary degrees from institutions including Pennsylvania State, University of Bordeaux, University of Helsinki, Finland (Koob, Janda).
A Collaborative and Focused Effort

To make progress against addictive disorders, the center will:

- Marshal an organized and focused collaborative research effort, turning the best scientific minds loose on the problem.
- Recruit and retain talented young investigators working in the area and support their initial efforts in research.
- Create a collaborative, interdisciplinary, synergistic environment that expands scientific thinking about addiction from many perspectives.
- Evaluate center-funded research aggressively on an annual basis to ensure that only promising pathways are pursued.
Supporting Innovative Research

Grants
- TSRI investigators submit requests for funding for innovative research.
- Accepted projects would receive funding to develop new approaches that will be then competitive for National Institutes of Health/National Science Foundation funding to continue the work.

Oversight
- A scientist-director holds an endowed chair to provide administration and scientific direction.
- An internal grant committee reviews the proposals and provides granting recommendations.
- A Scientific Advisory Board monitors the progress and research integrity of the center, reviews and evaluates work in progress, and issues recommendations concerning the continuation or discontinuation of projects.
Funding

The Addiction Research Center of Excellence will be funded by contributions totaling $40 million.

Expenditure plan:

- $9 million—Endowed chairs for four senior investigators (including one director)
- $10 million—Recruitment packages of $2 million each to recruit five new faculty members
- $3 million—New cutting-edge equipment
- $3 million—One-year grants of $330K to investigators seeking other sources of funding
- $15 million—A ten-year term endowment to ensure resources are available to follow up on the most promising findings, for example with clinical trials
A Lasting Contribution

Contributions will support world-class talent and equipment and fund innovative research projects to combat addictive disorders. These studies will transform what was once considered beyond the reach of medicine into a manageable disease that can be effectively treated—saving lives, sparing families and creating healthier communities.
Appendices
Appendix 1: Drugs Developed from TSRI Discoveries

- **Humira®** for rheumatoid arthritis, plaque psoriasis, Crohn’s disease, ulcerative colitis and other inflammatory conditions
- **Benlysta®** for lupus, a debilitating autoimmune disease
- **Leustatin®** for hairy cell leukemia, an unusual cancer of the blood
- Purification of **Factor VIII** for the bleeding disorder hemophilia
- **Vyndaqel®** for transthyretin familial amyloid polyneuropathy (TTR-FAP), a rare, progressive and fatal neurodegenerative disease
- **Surfaxin®** for infant respiratory distress syndrome, a life-threatening condition affecting pre-term infants
- **Cyramza®** for gastric and non-small cell lung cancer
- **Unituxin™** for the childhood cancer neuroblastoma
Appendix 2: Companies from TSRI Technology or Faculty

2014
- Aldabra Biosciences
- Padlock Therapeutics
- Transplant Genomics, Inc.

2013
- Blackthorn Therapeutics Inc.
- iGenomix
- Sirenas Marine Discovery
- Zebra Biologics

2012
- Abide Therapeutics
- Cypher Genomics
- Vesper Biologics

2011
- RQx Pharmaceuticals

2010
- Ember Therapeutics
- Epic Science

2009
- Receptos Pharma
- Protix, Inc.
- Zyngenia

2008
- aTyr Pharma
- Curna

2007
- Eyecyte, Inc.
- Fate Therapeutics
- Proteostasis Therapeutics
- Sapphire Energy

2006
- Affinity Pharmaceuticals
- Calmune
- Virome LLC
- Wittycell S.A.S.

2004
- Achaogen Inc.
- Motility, Inc.
- Promosome
- Rincon Pharmaceuticals (acquired by Sapphire Energy)

2003
- Ambrx Inc.
- FoldRx Pharmaceuticals
- Prion Solutions (acquired by Chiron)

2002
- CovX Research (acquired by Pfizer)
- NanoRX (acquired by Adaptive Therapeutics)
- VAXDesign (acquired by Sanofi Pasteur)
Appendix 2 - continued

2001
- Kalypsys
- Phenomix
- Syrxx (acquired by Takeda)

2000
- ActivX Biosciences (acquired by Kyorin)
- Neurome

1999
- Geneformatics (merged with Structural Bioinformatics)
- Optimer Pharmaceuticals
- Prolifaron (acquired by Alexion Pharmaceuticals)

1997
- Epicyte (acquired by Biolex Therapeutics)

1996
- Digital Gene Technologies (purchased by Neurome)
- Discovery Labs (merged with Acute Therapeutics)
- Drug Abuse Sciences
- Sangamo Biosciences

1995
- PharMore
- Thrombosys

1994
- Apovia AG (formerly EVAX Technologies, originally Immune Complex Corp.)

- Applied Molecular Evolution (formerly Lxsys; acquired by Lilly, Inc.)
- CombiChem (acquired by Dupont-Merck Pharmaceutical and merged with Bristol-Myers Squibb)

1993
- Ciphergen Biosystems (acquired by Bio-Rad Laboratories)

1992
- Sequel Therapeutics (later acquired by Cytel, which was subsequently spun-out as Epimmune)

1989
- Avanir Pharmaceuticals (formerly Lidak)
- Corvas (acquired by Dendreon Corporation)
- UNASYN

1986
- MP Biomedicals (formerly Qbiogene and Bio101)
- NeoMPS (formerly Multiple Peptide Systems)

1984
- Stratagene

1982
- Synbiotics

1981
- Quidel
# Appendix 3

## Therapeutic Pipeline

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<th>COMPOUND</th>
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## Appendix 3 continued

### AMBRYX PRODUCTS
- ARX-201  Growth Deficiency  Ambrx
- ARX-424  Autoimmune  Ambrx
- ARX-618  Diabetes  Ambrx
- ARX-328  Lipodystrophy  Ambrx

### OTHER EARLY STAGE PRODUCTS
- IC-14  Respiratory  Implicit
- ALT-801  Oncology  Altor
- Shok-Pak  Organ Failure  InflammaGen
- RG-2833  Friedreich’s Ataxia  BioMarin
- HSC-835  Oncology  Novartis
- 3K3A-APC  Cardiovascular  ZZ Biotech
- VS-4718  Oncology  Verstem
- Resokine-IV  Autoimmune  aTyr