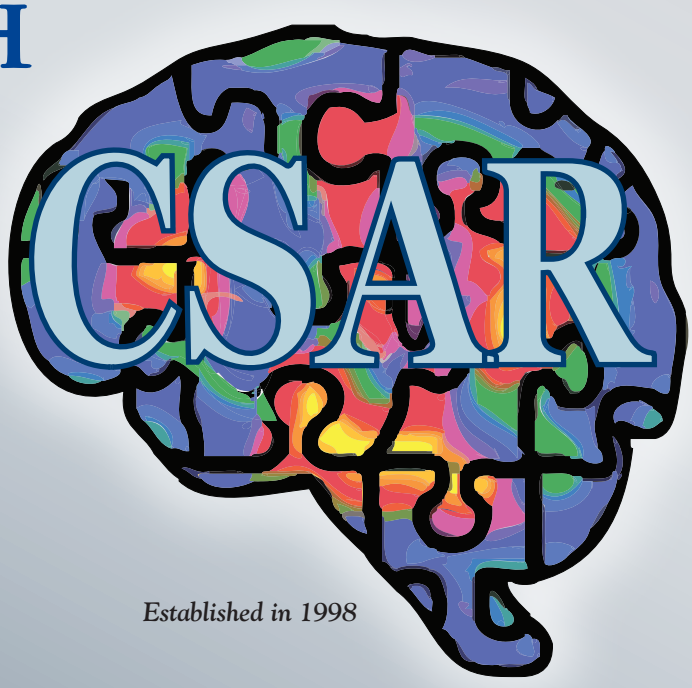
REPORT OF ACTIVITIES
2017-2019

TEMPLE UNIVERSITY

Lewis Katz School of Medicine

CENTER FOR SUBSTANCE ABUSE RESEARCH



Established in 1998

Table of Contents

History of the Center for Substance Abuse Research (CSAR) . . . . 2 - 3

Mission of the Center for Substance Abuse Research . . . . . 4 - 5

CSAR and the NIDA P30 Center 6

Organizational Structure of CSAR 7

P30 Center on Intersystem Regulation by Drugs of Abuse 8

CSAR Faculty 9

CSAR Faculty Research Interests . . . . . 10 - 23

CSAR Research Highlights . . . . . 24 - 32

CSAR Faculty Activities and Honors . . . . . 33 - 41

Grants Related to Substance Abuse
Awarded to Researchers in CSAR . . . . . 42 - 49

Publications . . . . . 50 - 65

History of the Center for Substance Abuse Research

The Center for Substance Abuse Research (CSAR) traces its roots to a collaborative research project involving members of the Department of Pharmacology. The project was carried out with funds from a grant from the National Institute on Drug Abuse (NIDA) entitled "Narcotic Receptors in Non-Addicted and Addicted States" with Dr. Martin W. Adler as the Principal Investigator. The initial focus of the research was on the neuropharmacology and neurophysiology of opioids and opioid receptors, with projects on the effects of morphine on body temperature, pain, the eye, and brain excitability in rodents. The scope of the studies expanded when the National Institute on Drug Abuse (NIDA) sought investigators who could examine the possible effects of opioids on the immune system. Results obtained from collaborations with members of the Department of Microbiology and Immunology demonstrated that morphine and other opioids were immunosuppressive, and the findings were published in the Proceedings of the National Academy of Sciences (1991:88:360-364). The new interdisciplinary efforts led to the award of a large grant from NIDA in 1991 to study these neuroimmune interactions.

As a result of a planning process undertaken by the School of Medicine examining new directions in research, steps were taken to create a formal Center at Temple University to study drugs of abuse. On May 11, 1998, CSAR was founded with Dr. Martin W. Adler, the Laura H. Carnell Professor of Pharmacology, as Director and Dr. Toby K. Eisenstein, Professor of Microbiology and Immunology, as Co-Director. Following the official founding of the Center, the affiliated faculty expanded rapidly to include members from the Departments of Biochemistry, Psychology, and Psychiatry. In 2000, CSAR was awarded a P30 Center Grant from NIDA, entitled "Center on Intersystem Regulation by Drugs of Abuse", to establish Core Laboratories in support of research in the area of drug abuse. This grant has been renewed three times, in 2005, 2010, and 2015. In October of 2008, Dr. Ellen M. Unterwald became Director of CSAR, and Dr. Adler assumed the title of Director Emeritus and Senior Advisor. Dr. Eisenstein remains as Co-Director. CSAR has evolved far beyond its original roots in the Department of Pharmacology and is now truly a multi-disciplinary, multi-department, multi-college enterprise, with faculty members drawn from many departments at the Medical School, as well as from the School of Pharmacy and the College of Liberal Arts. Using approaches that range from molecular biology to behavioral analyses, *in vitro* to *in vivo*, and single cell to animal to human, the 31 faculty members of the Center are investigating the effects of a variety of addictive drugs on the nervous and immune systems, and the mechanisms involved in their diverse biological actions.

History of the Center for Substance Abuse Research

At its founding in 1998, a small amount of space was assigned to CSAR for administrative offices and two Core Laboratories. At that time, faculty elected to join CSAR, but their laboratory and office spaces remained in their home departments. A major advance occurred in 2007, when interested faculty became eligible to receive official secondary appointments in CSAR, approved by their department chairs and by the Dean of Temple University School of Medicine. In May 2012, due to its highly successful research program, CSAR was assigned offices and laboratory space on the eighth floor of the new Medical and Education Research Building of the Medical School (pictured below). This architecturally attractive, state-of-the-art research and educational space now houses fourteen CSAR faculty members, as well as the Core Laboratories of the NIDA-funded P30 Center of Excellence. The floor is shared with research faculty from the Department of Pathology and Laboratory Medicine, all of whom have appointments in the Center. The consolidation of CSAR faculty and laboratories into contiguous space has raised the visibility of the Center, increased the cohesiveness of the faculty, trainees, and staff, and has promoted increased collaborations. Temple University School of Medicine was renamed the Lewis Katz School of Medicine at Temple University in 2015.

Mission of the Center for Substance Abuse Research

Prologue

Drug abuse is a major public health problem in the United States and worldwide. Not only does addiction damage the ability to live a normal life, but it also increases the incidence of infectious diseases including HIV, hepatitis C and tuberculosis. The biological basis for addiction is not completely understood but through basic research, immense progress has been made in elucidating neuronal circuits that mediate drug reward and neuroadaptations that occur during repeated drug exposure. Such changes in the brain lead to compulsive drug-seeking behaviors that form the basis of addictive disease. Similar to other diseases, such as heart disease and cancer, there can be no doubt that advances in understanding the biological underpinnings behind these conditions is essential to advance treatment and prevention strategies. It was researchers funded by grants from the National Institute on Drug Abuse (NIDA) who discovered opioid receptors followed by isolation of their endogenous ligands, as well as the cannabinoid receptors and endocannabinoids. These discoveries have opened up new vistas in our appreciation of neuronal circuitry controlled by opioids and cannabinoids that relate to addiction and perception of pain. Interestingly, the receptors for opioids and cannabinoids have been shown to be present not only on neurons, but also on cells of the immune system in the periphery and on microglia in the brain. Discoveries in this area have demonstrated a role for opioid and cannabinoid circuits in regulating immune responses, resistance to infection, and inflammation, with an increased awareness of the important interactions between the brain and the immune system. For example, CSAR faculty have shown that products of the immune system can modulate the function of opioid and cannabinoid receptors, as well as dopamine transmission, resulting in altered sensations of pain, body temperature, and drug-seeking behaviors. Continued basic research is critical to effectively prevent and treat substance abuse and dependence, as well for the discovery of new and better therapies for pain.

Mission Statement

The mission of CSAR is to carry out research to understand the biological basis of drug addiction and other effects of drugs of abuse that result in altered states of biological function. Knowledge gained about these drugs and the endogenous pathways they impact is important to prevent and successfully treat addictions, to alleviate human suffering through amelioration of pain and inflammation, and to reduce the medical consequences of substance abuse. Through the strength of our faculty and research, CSAR is a premier resource on the biology of addiction and avenues for development of new therapies for these devastating conditions.

Mission Scope

CSAR researchers are making discoveries in the following areas: 1) novel therapeutics to reduce relapse to drug-seeking behaviors, 2) molecular and genetic mechanisms that control expression of receptors and their endogenous ligands that are acted on by drugs of abuse, 3) receptor-ligand interactions and signaling mechanisms that initiate and control cellular responses to drugs of abuse, 4) neuronal circuits involved in

addiction-related behaviors, 5) behavioral and physiological consequences of exposure to drugs of abuse, 6) interrelationships between the nervous and immune systems and their receptors and products, 7) impact of exposure to addictive drugs on immune status and resistance to infection, including HIV, 8) the effects of drugs of abuse and the endogenous pathways they impact on physiological states including craving, anxiety, and depression, 9) the potential deleterious and beneficial interactions produced by drug combinations, and 10) pain and analgesia. Research in CSAR encompasses many classes of drugs including opioids (*e.g.,* heroin, morphine, oxycodone, fentanyl, buprenorphine), cannabinoids (*e.g.*, marijuana, phyto-cannabinoids, synthetic cannabinoids), psychostimulants [*e.g.*, cocaine, amphetamines, MDMA, cathinones found in "bath salts'\"], nicotine, and alcohol. The study of drug combinations constitutes an important area of research in CSAR, as polydrug use is a common clinical aspect of substance abuse. Drug combinations also are important tools as therapeutics.

A unique aspect of the research being carried out in CSAR is an emphasis on neuroimmune interactions as they relate to drugs of abuse. Strong collaborations between immunologists and pharmacologists/physiologists in the Center have revealed a bidirectional communication between chemokines, which are traditionally considered products of the immune system, in regulating signaling by opioid and cannabinoid receptors in the nervous system, and conversely, by opioids and cannabinoids in regulating signaling by chemokines in the immune system. Consequences of these interactions relate to perception of pain, generation of inflammation, and HIV infection. Chemokines also have been found to regulate classical neurotransmitter systems in the brain and through this mechanism can impact the actions of many drugs of abuse.

Education and Mentoring

An important part of the mission of the Center for Substance Abuse Research is to educate the next generation of scientists in the area of substance abuse research. Faculty in the Center mentor high school, undergraduate, graduate and medical students, and postdoctoral fellows and visiting scientists in their laboratories. Some of the students and postdoctoral fellows are supported by a Training Grant from the National Institute on Drug Abuse (NIDA/NIH) entitled "Drugs of Abuse and Related Neuropeptides." The Training Grant has been active for over 30 years and has made a huge impact on the education of young scientists at Temple University. The energy and enthusiasm of the trainees and their capacity to interface with each other result in a vibrant research and educational atmosphere. CSAR has established several activities that formalize and encourage these interactions. There is a biweekly journal club in which students and postdoctoral fellows present recent papers in the field. The Center sponsors a biweekly seminar series where leading scientists from around the world talk about their current research. Students and fellows have the opportunity to interact and network with the visiting investigators. A monthly work in-progress meeting promotes lively discussions about current research projects and offers an opportunity for trainees at all levels to present their findings. The Training Grant holds an annual all-day retreat where trainees give formal oral presentations of their research. In addition, students and postdoctoral fellows present their research in poster format at the biennial CSAR retreats. These activities provide opportunities for trainees to interact with CSAR faculty, students and postdoctoral fellows. In addition, CSAR faculty, postdoctoral fellows and students engage in scientific outreach activities to the community at large. Overall, the open and collegial atmosphere in CSAR leads to discussion and cross-fertilization of ideas between faculty and trainees at all levels, as well as excellent mentoring of the trainees by the CSAR research community.

CSAR and the NIDA Core Center of Excellence

The figure below illustrates the scope of the Center for Substance Abuse Research (CSAR). CSAR is represented as an umbrella, providing a focus for research, training, and education in the field of substance abuse. The drops below the umbrella highlight the research areas where CSAR investigators are studying addiction and other biological effects of drugs of abuse. CSAR investigators utilize state-of-the-art, multidisciplinary approaches to address important questions in each of the research areas noted under the umbrella. CSAR is the recipient of a grant from NIDA that funds a Core Center of Excellence (P30), entitled "Center on Intersystem Regulation by Drugs of Abuse". As detailed in the next section, this Center grant supports Core Laboratories run under the direction of CSAR faculty, for the purpose of enhancing research on drugs of abuse and addiction at local and national levels. In a subsequent section of this report, a table lists the grants awarded to CSAR faculty during the period of 2017-2019, totaling over $82 million, which represent support for research directly related to substance abuse. While the Core Center of Excellence grant from NIDA is substantial and has helped to integrate and expand the research of CSAR faculty, it should be appreciated that the CSAR is a much larger entity than the NIDA Core Center of Excellence. In the diagram below, this concept is depicted graphically. The Core Center of Excellence (P30) is shown on the pedestal of the umbrella, as it is one part of the support for the activities of CSAR.

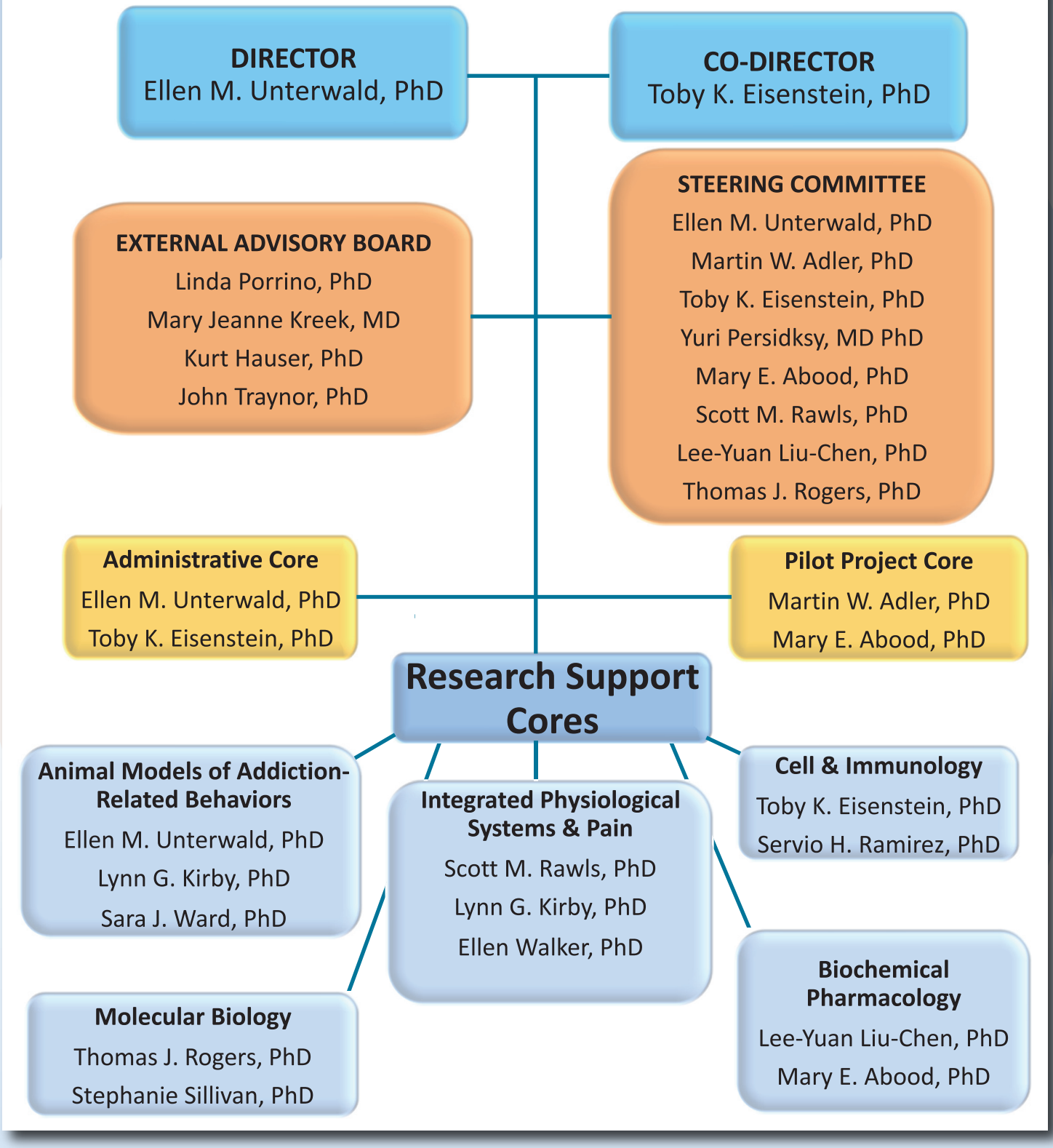
Organizational Structure of CSAR and the NIDA Core Center of Excellence

The Center for Substance Abuse Research (CSAR) was established under the direction of Dr. Martin Adler in 1998. He guided CSAR until 2008 when he voluntarily became Director Emeritus and Senior Advisor, passing the reins to Dr. Ellen Unterwald, the current Director of CSAR. Dr. Toby Eisenstein served as Co-Director with Dr. Adler and remains as Co-Director. The Director reports directly to the Dean of the School of Medicine. A Steering Committee that is composed of senior faculty in the Center provides guidance to the Director and the Center. Temple University faculty can receive official secondary appointments in CSAR by mutual agreement of the Steering Committee, the individual's Department Chair, and the Dean of the Medical School. Currently, 31 faculty have appointments in CSAR. CSAR faculty come from 11 departments of the Lewis Katz School of Medicine, one from the School of Pharmacy, and one from the College of Liberal Arts.

In 2000, the Center for Substance Abuse Research was awarded a Core Center of Excellence grant (P30) from the National Institute on Drug Abuse (NIDA) entitled, "Center on Intersystem Regulation by Drugs of Abuse". This grant was successfully renewed in 2005, 2010 and again in 2015. The NIDA P30 Center consists of seven Cores (Administrative, Animal Models and Behavioral Testing, Biochemical Pharmacology, Cell and Immunology, Integrative Pharmacology, Molecular Biology and Pilot Project Cores). The function of the Cores is to support and expand the scope of research on substance abuse and addiction. The objectives of the NIDA P30 Core Center are to enhance the overall productivity, synergy, and integration of interdisciplinary research in the field of substance abuse research, and to encourage additional investigators to conduct research in the area of addiction biology. The P30 Core Center of Excellence is one means by which the research of CSAR members is facilitated. Each Core has a Core Director who is responsible for the scientific work performed in that Core. A P30 Steering Committee provides oversight and is composed of the Core Directors, the Center Director, Co-Director, and Director Emeritus. In addition, there is a Scientific Coordinator and an External Advisory Committee. The External Advisory Committee is composed of leaders in the field of substance abuse research. This Committee aids in formulating long-range goals, evaluating progress and advising the Directors.

The NIDA P30 Core Center enhances research productivity and synergy by enabling the use of technologies and approaches that may not be available in individual researchers' laboratories. The Cores serve not only Temple University researchers, but investigators across the country, hence serving as a national resource to the substance abuse research community at large. The Cores have the capacity to perform a wide range of techniques spanning measurements of animal physiology and behaviors, to application of biochemical and molecular techniques to assess mechanisms of action of various drugs in the nervous and immune systems. The scope of activities carried out in the Cores encompasses all aspects of the Mission of CSAR, which is described earlier in this Report. The NIDA Core Center of Excellence has been a major force in facilitating productive collaborations that have carried research in the area of drugs of abuse to new heights. The goal of the Core Center and of CSAR is to provide an environment that will result in the highest quality, innovative, state-of-the-art research, making Temple a national resource for advancements in the field of addiction biology.

P30 Center on Intersystem Regulation by Drugs of Abuse



CSAR Faculty – 2019

Name	Department	School/College
Unterwald, Ellen M., Ph.D., *Professor & Director, CSAR*	**Pharmacology**	**Medicine**
Eisenstein, Toby K., Ph.D., *Professor & Co-Director, CSAR*	**Microbiology & Immunology**	**Medicine**
Adler, Martin W., Ph.D., *Laura H. Carnell Professor, Emeritus; Director Emeritus & Senior Advisor, CSAR*	**Pharmacology**	**Medicine**
Abood, Mary, Ph.D., *Professor*	**Anatomy & Cell Biology**	**Medicine**
Bangasser, Debra, Ph.D., *Associate Professor*	Psychology	Liberal Arts
Barbe, Mary, Ph.D., *Professor*	Anatomy & Cell Biology	Medicine
Barrett, James., Ph.D., *Adjunct Professor*	**CSAR**	**Medicine**
Brailoiu, Eugen, M.D., *Associate Professor Research*	**CSAR**	**Medicine**
Briand, Lisa, Ph.D., *Assistant Professor*	Psychology	Liberal Arts
Chong, Parkson Lee-Gau, Ph.D., *Professor*	Medical Genetics and Molecular Biochemistry	Medicine
Cowan, Alan, Ph.D., *Professor Emeritus*	**Pharmacology**	**Medicine**
Ho, Wenzhe, M.D., M.P.H, *Professor*	Pathology & Laboratory Medicine	Medicine
Kelsen, Steven, M.D., *Professor*	Pulmonary & Critical Care Medicine	Medicine
Kirby, Lynn, Ph.D., *Associate Professor*	**Anatomy & Cell Biology**	**Medicine**
Liu-Chen, Lee-Yuan, Ph.D., *Professor*	**Pharmacology**	**Medicine**
Morrison, Mary, M.D., M.S., *Professor & Vice Chair for Research*	Psychiatry	Medicine
Muschamp, John, Ph.D., *Assistant Professor*	**Pharmacology**	**Medicine**
Parikh, Vinay, Ph.D., *Associate Professor & Director Neuroscience Program*	Psychology	Liberal Arts
Persidsky, Yuri, M.D., Ph.D., *Professor & Chair*	Pathology & Laboratory Medicine	Medicine
Potula, Raghava, M.H.A., Ph.D., *Associate Professor*	Pathology & Laboratory Medicine	Medicine
Ramirez, Servio, Ph.D., *Associate Professor*	Pathology & Laboratory Medicine	Medicine
Rawls, Scott, Ph.D., *Professor*	**Pharmacology**	**Medicine**
Reichenbach, Zachary, M.D., Ph.D., Fellow	Gastroenterology & Hepatology	Medicine
Rogers, Thomas J., Ph.D., *Professor & Director*	Pharmacology & Center for Inflammation, Translational and Clinical Lung Research	Medicine
Rom, Slava, Ph.D., *Assistant Professor*	Pathology & Laboratory Medicine	Medicine
Sawaya, Bassel, Ph.D., *Professor*	Neurology & Fels Institute for Cancer Research and Molecular Biology	Medicine
Sillivan, Stephanie, Ph.D., *Assistant Professor*	**Anatomy & Cell Biology**	**Medicine**
Tuma, Ronald, Ph.D., *Professor*	**Physiology**	**Medicine**
Walker, Ellen, Ph.D., *Professor and Chair*	Pharmaceutical Sciences	Pharmacy
Ward, Sara Jane, Ph.D., *Assistant Professor*	**Pharmacology**	**Medicine**
Wimmer, Matthieu, Ph.D., *Assistant Professor*	Psychology	Liberal Arts

***Bolded names designate CSAR as their primary affiliation. All other appointments in CSAR are secondary appointments.**

CSAR Faculty Research Interests

Mary Abood, Ph.D.

Professor, Department of Anatomy & Cell Biology, Lewis Katz School of Medicine

Dr. Abood and her laboratory are investigating the endocannabinoid system with particular focus on the molecular pharmacology of the receptors. The endocannabinoid system is thought to play a role in addiction, pain regulation, motor control, learning, and memory, as well as in regulating immune function and bone growth. Dr. Abood's laboratory uses cloned cannabinoid receptors, CB1 and CB2, expressed in cell systems to identify the structural and concomitant functional features of these receptor molecules. The studies are designed to elucidate the molecular mechanisms of CB receptor action. Recent studies have focused on allosteric modulation of the CB1 receptor, to reveal potential sites in the molecule that could be therapeutic targets. In addition, Dr. Abood is engaged in identifying novel cannabinoid receptor subtypes. GPR55 was initially proposed to be a candidate cannabinoid receptor, but her laboratory has found that, while it shares some ligands with CB1 and CB2, a unique set of ligands interacts with GPR55. Through the use of these ligands, a role for GPR55 in pain perception has been uncovered. Other recent studies on GPR18 suggest that it also may be a receptor for endocannabinoids.

Martin W. Adler, Ph.D.

Director Emeritus and Senior Advisor, CSAR
Laura H. Carnell Professor Emeritus, Department of Pharmacology,
Lewis Katz School of Medicine

Dr. Adler's laboratory has had a primary focus for many years on the study of opioids in terms of their effects on thermoregulation, analgesia, and brain excitability. The effects of cannabinoids on analgesia and body temperature have also been studied. The endogenous opioid system interacts with the cannabinoid system, often resulting in a potentiated effect on both body temperature and analgesia. Furthermore, the kappa opioid system is essential for both cannabinoid and opioid-induced hypothermia. A more recent interest of Dr. Adler's group has been neuroimmune pharmacology. His laboratory has demonstrated that there is heterologous desensitization of the respective receptors for opioids and chemokines in the brain, which is manifested as reduced analgesia and thermoregulatory responses. Similarly, chemokines can desensitize cannabinoid responses to pain and temperature in the brain. The evidence supports a model where these products of the immune system can block the actions of opioids and cannabinoids by interfering with their respective receptor signaling. Dr. Adler proposed a theory of brain communication involving chemokines in neuron-to-neuron and in neuron-to-glia signaling. Further, he proposed that the study of the interactions of the chemokine system with the opioid and cannabinoid systems may lead to new therapeutic approaches for the treatment of conditions as varied as inflammatory pain, neurodegenerative diseases, head trauma, and addiction. Dr. Adler's current work has shown that the combination of chemokine receptor antagonists with sub-optimal analgesic doses of morphine, oxycodone or meperidine can achieve maximal analgesia in several different pain assays in rodents. This opioid-sparing strategy can potentially be used to achieve effective pain relief with fewer side-effects at lower doses of opioid analgesic drugs.

Debra A. Bangasser, Ph.D.

Director, Neuroscience Program in the College of Liberal Arts
Associate Professor, Department of Psychology, Temple University

There are sex differences in most psychiatric disorders, including depression and substance use disorders. Stress is an environmental factor that can precipitate psychiatric disease. As principal investigator of the Neuroendocrinology and Behavior Laboratory, Dr. Bangasser uses techniques from behavioral neuroscience, neuroendocrinology, and cellular and molecular biology to investigate whether there are neurobiological factors that contribute to this disparity in psychiatric disorders between men and women. Specifically, her research program explores sex differences in stress response systems, including corticotropin releasing factor, that bias females towards hyperarousal and males towards cognitive deficits. She also examines how early life adversity can contribute to sex-specific disease vulnerability and resilience to motivated behavior.

Mary Barbe, Ph.D.

Professor, Department of Anatomy & Cell Biology, Lewis Katz School of Medicine

Dr. Barbe's laboratory developed a unique voluntary rat model of Work-Related Musculoskeletal Disorders with varying levels of voluntary repetition and force employed, and have characterized the short-term effects of repetitive strain injury in this model. She is examining the long-term effects of repetitive and/or forceful tasks on musculoskeletal and nervous system pathophysiology, focusing on inflammatory and fibrotic endpoints, and on how these processes induce degenerative tissue changes and sensorimotor dysfunction. She is currently exploring translatable pharmaceutical treatments to block fibrotic processes, and the associated sensorimotor declines. Specifically, she is exploring the effectiveness of an anti-Connective Tissue Growth Factor (CTGF/CNN2) monoclonal antibody (FG-3019, pamreluvmab) and a specific neurokinin 1 receptor antagonist that blocks Substance P signaling for either blocking the development of fibrogenic processes or reversing established fibrosis. Additionally, in collaboration with Dr. Michael Ruggieri in the Department of Anatomy and Cell Biology, Dr. Barbe is examining means of successful re-innervation of bladder and urethral sphincter targets after spinal root injury, and the peripheral and central neuroplasticity induced by this re-innervation surgery.

James E. Barrett, Ph.D.

Adjunct Professor, CSAR, Lewis Katz School of Medicine

Dr. Barrett is a behavioral pharmacologist with a long-standing interest in substance abuse research. His early academic research, conducted in squirrel monkeys, demonstrated that drugs of abuse can have behavioral effects that depend overwhelmingly on behavioral history, the environmental context, and on pharmacological experience. In many cases, these "non-pharmacological" determinants of drug action were shown to produce qualitatively different effects on behavior. These effects were not specific to one class of drugs as they were found with opioids, psychomotor stimulants as well as benzodiazepines, and have implications for understanding the etiology of substance use disorders. Drugs of abuse do not have immutable properties and their effects on behavior can depend critically on non-pharmacological variables. Dr. Barrett also has had wide experience in the pharmaceutical industry, having served as Vice President of Neuroscience research at Wyeth, as Chief Scientific Officer and President of Research and Development at Adolor Corporation, where he directed discovery research while also overseeing the clinical development and regulatory filing for the FDA-approved drug alvimopan (Entereg®), a peripherally restricted mu- opioid receptor antagonist for the treatment of postoperative ileus. He also served as Sr. Vice President of Research

at Memory Pharmaceuticals, a company founded by the Nobel Laureate Eric Kandel. He returned to academia at Drexel University College of Medicine where he became Chair of the Department of Pharmacology and Physiology, Founding Director of the M.S. Program in Drug Discovery and Development as well as the Founding Director of Drexel University's Clinical and Translational Research Institute. His current research, conducted in collaboration with Mebias Discovery and funded by the National Institute on Drug Abuse, is focused on the pharmacology of 'biased' mu opioid receptor agonists as potential analgesics that are devoid of the side effects typically associated with these compounds.

Eugen Brailoiu , M.D.

Associate Professor Research, CSAR, Lewis Katz School of Medicine

Dr. Brailoiu's research focus is on calcium signaling and dysregulation of calcium pathways by drugs of abuse. Calcium plays a critical role in cellular functions including membrane excitability, neurosecretion, nitric oxide (NO) and reactive oxygen species (ROS) synthesis, and gene expression. There are two major ongoing projects: 1) to investigate the calcium component involved in cocaine addiction, and 2) to investigate the calcium pathways affected by cocaine in non-excitable cells with focus on the blood-brain barrier. Dr. Brailoiu's laboratory has published that Sigma-1 R/IP3/TRPC pathways play a critical role in cocaine activation of D1-expressing neurons from the nucleus accumbens. Furthermore, the Sigma-1 R/Store-Operated-Calcium Entry (SOCE) crosstalk is involved in cocaine action in non-excitable cells. The goal of the projects is to identify potential targets for treatment of cocaine addiction. Very recently, Dr. Bralioiu's group identified that choline is a second messenger (like cAMP, NO, IP3) that activates Sigma-1R. They will further investigate the role of choline-Sigma 1R in drug addiction. Dr. Brailoiu's laboratory uses various techniques to test drug effects on dissociated and cultured primary cells, including neurons, such as fluorescent and electrophysiological measurements, as well as molecular approaches.

Lisa Briand, Ph.D.

Assistant Professor, Department of Psychology and Program in Neuroscience, College of Liberal Arts

The major driving force behind cocaine relapse is drug craving. The most widely accepted preclinical model to study this craving involves training animals to self-administer drugs, extinguishing this responding by removing the drug reinforcer, and subsequently eliciting reinstatement of responding. Stressful experiences and cues previously paired with drug use elicit craving in human addicts and reinstate extinguished cocaine-seeking behavior in this reinstatement model. Dr. Briand and members of her laboratory utilize a variety of techniques including behavioral pharmacology, mouse genetics, molecular biology, and electrophysiology to study how the brain responds differently to stress and cues after a cocaine self-administration experience. Following chronic cocaine exposure, neuroadaptations occur in the glutamatergic neurotransmitter system. Among these are alterations in the composition of one type of glutamate receptor, the AMPA receptor. Activity-dependent insertion and removal of AMPA receptors represents a critical form of synaptic plasticity. This activity-dependent AMPA receptor trafficking is mediated by many second messenger systems and scaffolding proteins. Current work, funded by the National Institute on Drug Abuse, examines the mechanisms by which zeta-inhibitory peptide is able to disrupt reinstatement of cocaine seeking, focusing on AMPA receptor trafficking mechanisms. An additional focus of Dr. Briand's work is examining how adolescent stress can lead to increased vulnerability to addiction. Stressful experiences during adolescence have been shown to increase drug use and addiction. This association may be due, in part, to the effect of these drugs on the developing adolescent brain, or be a direct result of stress permanently altering neurophysiology during adolescence. Current work in the laboratory is aimed at examining how adolescent stress alters the brain's response to cocaine during adolescence and adulthood.

Parkson Lee-Gau Chong, Ph.D.

Professor, Department of Medical Genetics and Molecular Biochemistry, Lewis Katz School of Medicine

Dr. Chong's research is focused on membrane biophysics and lipid membrane-based biotechnology. Dr. Chong investigates how cholesterol, phospholipids and peptides/proteins (e.g., gramicidins) are organized in model and cell membranes and how membrane organization affects ligand-receptor binding, drug (e.g., combretastatin A4 disodium phosphate) partitioning and release, membrane behaviors of lipid-soluble anti-oxidants (e.g., lipoic acid), and cellular signal transduction. In the project related to biotechnology, Dr. Chong's group is developing novel liposomes and tailoring naturally occurring archaea microvesicles that are extremely stable at body temperature, yet capable of responding to extrinsic stimulations (e.g., hyperthermia treatment), to conduct target delivery and controlled release of small drug molecules or miRNA for anti-cancer or anti-thrombotic purposes. In addition, his group, in collaboration with bioengineering scientists, designs, fabricates, and characterizes novel free-standing planar membrane systems in micro-devices for applications such as artificial photosynthesis and biosensing.

Alan Cowan, Ph.D.

Professor Emeritus, Department of Pharmacology, Lewis Katz School of Medicine

Dr. Cowan was initially employed in industry by Reckitt-Coleman (later Reckitt Benckiser) where he was the co-developer of buprenorphine. Currently, at Temple, Dr. Cowan studies the relationship between itch and pain in mice and rats. His laboratory, in collaboration with a Senior Scientist in CSAR, Saadet Inan, has been instrumental in developing the concept that the kappa opioid receptor is fundamental in the anti-itch process. Recent studies have shown the utility of nalbuphine, a clinically used kappa agonist as a global antipruritic, with efficacy against a range of itch-inducing agents and conditions. Using models involving chemically induced scratching in mice, new compounds are being investigated that target the itch of human liver disease, as well as that of HIV.

Toby K Eisenstein, Ph.D.

Co-Director, Center for Substance Abuse Research
Professor, Department of Microbiology & Immunology, Lewis Katz School of Medicine

The major research areas in Dr. Eisenstein's laboratory involve investigation of neuroimmune circuits that relate to abused substances. She has published extensively showing that opioids and cannabinoids suppress functional immune responses and sensitize to various bacterial infections when given *in vivo* or *in vitro*. She found that tolerance develops to this opioid-mediated immunosuppression, and subsequent withdrawal from morphine induces profound immunosuppression through effects on macrophages and B-cells. Her laboratory was the first to show that morphine induces sepsis in mice, and also sensitizes to oral infection with the enteric murine pathogen, *Salmonella typhimurium*, and systemic infection with the opportunistic pathogen, *Acinetobacter baumannii.* She has carried out mechanistic studies on the effect of morphine and morphine withdrawal on cytokine and chemokine profiles including IL-12, IL-17A, TGF-β, and IL-1β, that correlate with immunosuppression and sensitization to infections. In addition, she has shown that cannabinoids with activity at the CB_2 receptor are immunosuppressive and inhibit T cells involved in skin and organ graft rejection through production of IL-10 and induction of T regulatory cells. A patent has been issued for use of CB2-selective agonists in inhibiting graft rejection. Her recent work has been in collaboration with Drs. Adler, Rawls, and Cowan on a Department of Defense-funded project to assess the effect of chemokine receptor antagonists (CRAs) on potentiating the analgesic capacity of morphine in

5 pain models in rodents. Results show that CRAs can shift the morphine dose-response curve significantly to the left in a rat model of incisional pain, and can also significantly augment the potency of morphine in the cold-water tail flick test and the formalin pain test. Her laboratory is determining the effect of these treatments on levels of chemokines and cytokines. She is Director of the Cell and Immunology Core of the National Institute on Drug Abuse P30 Center of Excellence grant. Through this Center she is collaborating with other faculty in determining the role of selected chemokines in cocaine and opioid addiction in rats.

Wenzhe Ho, M.D., M.P.H.

Professor, Department of Pathology & Laboratory Medicine; Department of Anatomy & Cell Biology, Lewis Katz School of Medicine

Dr. Ho is interested in the interplay between drugs of abuse, host innate immunity and HIV infection. His studies explore new strategies to activate/induce intracellular antiviral factors against HIV in both immune and non-immune cells. He uses *in vitro* and *ex vivo* models as well as clinical specimens to address three important questions: A. Do drugs of abuse suppress host cell innate immunity and facilitate HIV infection? B. Do drugs (opioids and methamphetamine) and/or HIV impair immune functions of macrophages and microglia, resulting in neuronal damage? C. Are non-immune cells at the primary HIV infection sites involved in host innate immune responses to HIV? To address these questions, Dr. Ho is pursuing a number of different approaches, including examining (1) whether opioids or methamphetamine impair host cell innate immunity and facilitate HIV infection; (2) the role of sensors of innate immunity (Toll-like receptors, RIG-I- and DNA sensors) of immune cells (T cells, monocytes/macrophages, and microglia) and non-immune cells (neurons and astrocytes) in the central nervous system (CNS), and in the gastrointestinal and female reproductive tracks (endothelial cells and epithelial cells) that recognize and control HIV infection/replication; and (3) the role of antiviral factors and mechanisms involved in protection of the CNS from HIV infection.

Steven Kelsen, M.D.

Professor, Department of Thoracic Medicine and Surgery, Lewis Katz School of Medicine

A major research area in Dr. Kelsen's laboratory is the role of the unfolded protein response (UPR) in the development and progression of Chronic Obstructive Pulmonary Disease (COPD). COPD is largely a consequence of chronic cigarette smoking. Chronic cigarette smoking causes endoplasmic reticulum stress and elicits an UPR in the human lung. The UPR relieves endoplasmic reticulum stress, a condition in which mis-folded proteins accumulate in the endoplasmic reticulum, by altering protein synthesis, folding, transport and degradation. Dr. Kelsen's studies indicate that endoplasmic reticulum stress signaling pathways are activated in the lungs of active smokers, and that endoplasmic reticulum stress is heightened even in ex-smokers. Failure to upregulate the hallmark UPR effectors in COPD indicates an aberrant UPR response. Dr. Kelsen has previously investigated the regulation of cytokine and chemokine expression in the human respiratory tract and the role of these molecules in the development of human lung disease. He has shown that structural cells in the respiratory tract express a variety of pro-inflammatory cytokines and chemokines, and receptors for the chemokine, CXCR3. This chemokine receptor is functionally active and regulates airway and alveolar epithelial cell chemotaxis and proliferation in the presence of its ligands, CXCL9, 10 and 11. Current research is examining the effect of chronic exposure to cigarette smoke on the regulation of expression of CXCR3 and its ligands in the human and mouse lung.

Lynn Kirby, Ph.D.

Associate Professor, Department of Anatomy & Cell Biology, Lewis Katz School of Medicine

Dr. Kirby's research focuses on the effects of stress and stress hormones on the serotonin [(5-hydroxy-tryptamine (5-HT)] system. Serotonin is a brain neurotransmitter that is involved in a wide range of behaviors, including emotional behaviors. Long-term exposure to stress is known to play a role in psychiatric disorders such as anxiety and depression. Stress is also a potent initiator of relapse in abstinent persons with a prior history of substance abuse. Currently, the laboratory is using *ex vivo* electrophysiological and chemogenetic approaches with drug self-administration models to examine the role of 5-HT circuits in opiate addiction and stress-induced relapse. Some of the clinical effects of stress may, in part, be mediated by 5-HT. In the laboratory, Dr. Kirby has examined the effects of stress and stress hormones on the electrical activity of 5-HT-containing cells in the brain and the release of 5-HT from nerve terminals in rodent models. She has found that stress has qualitatively different effects on 5-HT neurotransmission depending on the brain region examined and the particular stressor that is employed. Previous studies also included investigation of the effects of chemokines, immune molecules in the brain, and their interactions with traditional neurotransmitter and neuropeptide systems (5-HT, dopamine, opioids and cannabinoids). Through collaborations with other investigators, the laboratory is also examining the physiological effects of cannabinoid and candidate cannabinoid receptor stimulation, and exploring cannabinoid effects on cognition, synaptic plasticity and inflammation in models of stroke and traumatic brain injury.

Lee-Yuan Liu-Chen, Ph.D.

Professor, Department of Pharmacology, Lewis Katz School of Medicine

Agonists of the kappa opioid receptor (KOR) are potentially useful as analgesics, without the abuse potential and respiratory depression associated with mu opioid receptor agonists. In addition, KOR agonists may be useful as antipruritic agents. However, development of KOR agonists has been limited by their side effects such as dysphoria, sedation and psychotomimetic effects, including hallucinations. Research in Dr. Liu-Chen's laboratory aims to determine the signaling mechanisms in the brain underlying the beneficial and detrimental effects of KOR agonists. Her group, together with Dr. Matthias Mann's laboratory in Germany, recently demonstrated by behavioral and phosphoproteomics approaches that the mTOR pathway was responsible for the aversive effects of KOR agonists, but not analgesia, anti-pruritic effects, hypolocomotion, or lack of motor coordination. One focus of the research is to discover KOR agonists with a lower propensity to cause unwanted side effects. In addition, ongoing research is examining the roles of agonist-induced KOR phosphorylation in KOR-mediated behaviors and signal transduction in various brain regions. These studies use a mutant mouse line expressing phosphorylation-deficient KOR or mouse lines with conditional knock-out of G Protein-Coupled Receptor Kinase 5 or 6 (GRK5 or GRK6). Moreover, the laboratory is characterizing neurons expressing KOR in the claustrum, which has the highest KOR density in the brain, in terms of their neuronal circuitry, neurotransmitters and functional roles in KOR-mediated behaviors. A recently generated knock-in mouse strain expressing a fusion protein of KOR conjugated with a tomato red fluorescent protein is being used in these studies. Characterization of wild-type and mutant mouse lines with conditional deletion of the KOR or expressing mutant KORs and injection of viral vector containing Cre recombinase into brain regions are among the planned approaches. In addition, Dr. Liu-Chen has discovered two previously unknown KOR-expressing pathways near the ventral median fissure, one on each side. She is investigating the origin and possible functions of these neuronal tracts. In these studies,

the laboratory employs behavioral tests (analgesia, anti-scratch, conditioned place aversion, hypolocomotion and motor incoordination), as well as biochemical pharmacology approaches (receptor binding, phosphorylation and internalization, phosphoproteomics,) and neuroanatomical techniques (CUBIC, CLARITY, immunohistochemistry, in situ hybridization, anterograde and retrograde neuronal tract tracing, confocal microscopy, 3D brain imaging).

Mary Morrison, M.D., M.S.

Professor & Vice Chair for Research, Department of Psychiatry and Behavioral Science, Lewis Katz School of Medicine

Dr. Morrison's research is in the area of comorbidity of substance abuse and mental health, and novel drugs for the treatment of substance use disorders. Her laboratory is currently focused on medication development for cocaine addiction. Fatal overdoses associated with cocaine are rapidly increasing in the US, and there are currently no effective treatment medications. Dr. Morrison is the Temple University Principal Investigator on studies of clavulanic acid for cocaine use disorders, in collaboration with Dr. Kyle Kampman, Professor of Psychiatry at the University of Pennsylvania, who is the Principal Investigator of the NIDA-funded Cocaine Medication Development Center. This study builds on the preclinical work of Dr. Scott Rawls, who has demonstrated that clavulanic acid inhibits the motivation to self-administer cocaine in rodent models.

Muschamp, John, Ph.D.

Assistant Professor, Department of Pharmacology, Lewis Katz School of Medicine

Dr. Muschamp studies the neurobiology of motivation, affect, and executive function and how they are altered in drug addiction using a combination of behavioral, pharmacologic, anatomic, and molecular approaches. Important modulators of mesolimbic dopamine transmission are hypocretin (orexin) and dynorphin peptides released by projections from the hypothalamus. Dr. Muschamp's NIH-funded research has shown that the hypocretin system potently excites the midbrain dopamine reward pathway, and that attenuated hypocretin signaling decreases the reinforcing effects of cocaine and natural rewards like sex behavior. Additionally, Dr. Muschamp has also established that decreased hypocretin transmission attenuates spontaneous- and cocaine-induced impulsive behavior. These effects appear to arise from the ability of hypocretin to modulate the aversive or depressive-like effects of hypocretin's co-transmitter dynorphin. Understanding the relationship and interactions between hypocretin and dynorphin is a major goal of Dr. Muschamp's research. Because disturbances in mood, motivation, and executive function often accompany addiction and other psychiatric illnesses (e.g. bipolar disorder), and may be mediated by disrupted function of the hypocretin-dynorphin system, Dr. Muschamp's work is designed to determine the utility of hypocretin receptor antagonists for the treatment of substance use disorders and other psychiatric illnesses characterized by high levels of impulsivity.

Vinay Parikh, Ph.D.

Associate Professor, Department of Psychology and CLA Neuroscience Program

Dr. Parikh is a behavioral neuroscientist who studies neuromodulation of attention and executive functions, and how these cognitive processes are impacted by genetic and environmental factors, long-term use of psychotropic drugs such as nicotine, and aging. Previous research from his laboratory showed that chronic nicotine and nicotine withdrawal differentially impact cognitive flexibility, and that these behavioral effects primarily occur due to neuroadaptive changes in discrete frontostriatal circuits. At the cellular level,

Dr. Parikh identified brain-derived neurotrophic factor (BDNF) as a key molecular substrate that alters these circuits by producing perturbations in glutamate signaling following chronic nicotine exposure. His research has emphasized that normalizing BDNF-trkB (the receptor for BDNF) during periods of nicotine abstinence make corticostriatal glutamate circuits more tolerant to the detrimental effects of withdrawal on cognition, which may reduce relapse rates among smokers. To understand why vulnerability to nicotine addiction significantly increases in individuals who begin smoking during adolescence, Dr. Parikh is investigating the effects of nicotine on neurobehavioral processes during developmental transitions. Recent work from his laboratory demonstrated that adolescent nicotine exposure produces a generalized increase in reinforcement sensitivity; however, this sensitivity becomes biased towards nicotine reinforcement in adulthood due to the impact of adolescent nicotine on impulsive behaviors. In collaboration with Dr. Toby Eisenstein, he is currently investigating the contribution of neuro-immune mechanisms on nicotine-induced alterations in the development of prefrontal cortex and adult cognition. Dr. Parikh has also collaborated with other CSAR investigators including Drs. Unterwald, Rawls and Bangasser.

Yuri Persidsky, M.D., Ph.D.

Professor and Chair, Department of Pathology & Laboratory Medicine, Lewis Katz School of Medicine

Dr. Persidsky's research program has multiple lines of investigation. Several projects relate to the effects of alcohol on HIV-1 CNS toxicity. His ongoing work delineates mechanisms of blood-brain barrier (BBB) injury in neuroinflammation associated with HIV-1 CNS infection and associated immune responses. Diminution of neuroinflammation constitutes a logical approach for prevention of HIV-1 and alcohol-mediated neurodegeneration. He is investigating beneficial effects of potential agonists at CB_2 cannabinoid receptors, which possess potent anti-inflammatory and neuroprotective properties. Dr. Persidsky's group proposes that CB_2 receptor activation will attenuate neuronal dysfunction and BBB injury caused by alcohol and HIV-1 via effects on monocytes, brain endothelium, activated microglia and HIV-1-infected macrophages**.** A MERIT award funded by the National Institute on Alcohol Abuse and Alcoholism supports this research direction. Another research project studies protective properties of secoisolariciresinol diglucoside (SDG), the main bioactive lignan phenolic in wholegrain flaxseed. Dietary SDG potently boosts endogenous antioxidant and anti-inflammatory activity in several tissues including the CNS. SDG and its metabolites cross the BBB and enter brain tissues, making it an attractive candidate for mitigation of HIV-induced neurotoxicity. In another project, Dr. Persidsky is addressing the combined effects of opioids and smoke exposure on the inflammatory response, particularly as it pertains to the development of neurodegeneration following HIV infection using a humanized mouse model of HIV-induced encephalitis. It is established that opioids regulate expression of several important pro-inflammatory chemokines and chemokine receptors (including CCR5 and CXCR4). Studies are also underway to assess the role of receptor cross-talk between chemokine and opioid receptors during HIV infection in the brain. This infection produces chemokines, leading to activation of the respective chemokine receptors and resulting in cross-desensitization of opioid receptors. The consequence of this set of events is an elevated sensitivity to pain stimuli. Dr. Persidsky is also using mouse models to evaluate the influence of HIV gp120 in the induction of neuroinflammation, including the associated neuropathic pain. Studies are also addressing the ability of morphine to attenuate the development of this pain response.

Raghava Potula, M.H.A., Ph.D.

Associate Professor, Pathology & Laboratory Medicine,
Lewis Katz School of Medicine
Medical Director, Clinical Microbiology and Immunology Laboratories,
Temple University Hospital

Dr. Potula's research interests encompass the intersection of the fields of drugs of abuse, immune modulation, and infectious disease. His laboratory studies the mechanisms that regulate immune homeostasis and plasticity in the setting of drugs of abuse and how such alterations affect host immune response to chronic viral infections. The overarching goal is to understand the mechanistic insight into many parameters that shape the functionality of the immune system in response to external cues. Ongoing studies are currently focused on the role of brain endothelial extracellular vesicles (EV) in the neuropathology of drugs of abuse and HIV in collaboration with Dr. Servio Ramirez. A second research theme involves exploring the neuroimmune mechanisms that modulate neurotrophic factors and other plasticity-related molecules in neurodegenerative processes. Neuroinflammatory disorders (including human immuno-deficiency virus-1 encephalitis, HIVE) are associated with oxidative stress and inflammatory brain injury, and excessive alcohol use or stimulant drugs can exacerbate tissue damage. Purinergic receptors expressed on the microglia have emerged as key mediators in several degenerative diseases involving neuroinflammatory components (such as ischemia, Alzheimer's Disease and experimental autoimmune encephalitis). Dr. Potula's recent studies have demonstrated that the purinergic receptors, P2X4 and P2X7R, play a role in regulating microglial function and, more importantly, mediate alcohol-induced effects and stimulant-induced microglial activation responses, respectively. A long-term objective of Dr. Potula's research is to understand how inappropriate regulation of peripheral immunity and resident elements of immunity in the central nervous system leads to disease, and how elements of immunity within or outside of the central nervous system can be manipulated to promote health.

Servio H. Ramirez, Ph.D.

Associate Professor, Pathology & Laboratory Medicine,
Lewis Katz School of Medicine

Dr. Ramirez's laboratory focuses on the study of how brain pathologies affect the neurovascular unit (NVU) and how these changes lead to the disruption of the Blood-Brain Barrier (BBB). His ongoing research includes the following areas of investigation: 1) assay development for next generation microfluidic modeling of the human NVU; 2) characterization of temporal and spatial changes of the cerebral vasculature during neuroinflammation; 3) serological biomarker discovery for evaluation of brain injury, and 4) use of biological and pharmacological intervention for repairing and protecting the NVU. Although key advances have been made in the complexity of microfluidic models of capillaries and small vessels, few approaches have accounted for the effects of essential blood components on the microvasculature. This paucity is especially striking in models of the blood-brain barrier (BBB), where interaction between blood components and the cells that form the NVU is crucial for mediating a broad range of neuropathologies characterized by barrier disruption and subsequent inflammation. Thus, part of Dr. Ramirez's research program is devoted to bringing to reality biomimetic *in vitro* human NVU models that can create a platform to test BBB disruption by drugs of abuse, measure drug CNS penetrability and evaluate promising interventions to heal dysfunction in the NVU. Dr. Ramirez's laboratory also has unique expertise in the area of biomarkers. Specifically, he has active projects funded by the NIH to evaluate extracellular vesicles (present in the blood) as biomarkers of neuroinflammation and as mediators of neuroinvasion by HIV-1-infected immune cells. In addition, the

Ramirez laboratory also heads a research initiative funded by the Pennsylvania Department of Health to study the link between brain injury and addiction susceptibility. His work has offered the first preclinical support for epidemiological findings that suggest that sustaining brain injury during adolescence may augment the rewarding effects of psychostimulants in adulthood.

Scott Rawls, Ph.D.

Professor, Department of Pharmacology, Lewis Katz School of Medicine

Dr. Rawls' laboratory uses vertebrate (rats, mice) and invertebrate (planarians) models to investigate the neuropharmacology of cocaine, opioids and designer "bath salt" synthetic cathinones. A primary focus is defining a role for corticolimbic glutamate transporters, especially glutamate transporter subtype 1 (GLT-1), in psychostimulant addiction. His laboratory has demonstrated that the FDA-approved β-lactamase inhibitor clavulanic acid can increase GLT-1 activity similar to ceftriaxone but with a more patient-friendly profile (*e.g.*, enhanced brain penetrability, minimal antibacterial activity, oral activity). Clavulanic acid is capable of reducing addiction-related effects of both morphine and cocaine in rats by decreasing glutamate transmission. This work provided the foundation for a clinical study that is being conducted through a collaboration involving Dr. Mary Morrison of Temple University Department of Psychiatry and the University of Pennsylvania. More recently, in collaboration with Dr. Allen Reitz, Dr. Rawls' laboratory has shown that troriluzole, a pharmaceutically beneficial prodrug of FDA-approved riluzole that activates GLT-1 and inhibits neuronal glutamate release, reduces relapse to both cocaine and opioids in rat self-administration studies. Other research by Dr. Rawls investigates the designer cathinones contained in a dangerous street drug called "bath salts". His laboratory is investigating the neuropharmacology of these synthetic cathinones (*e.g.,* mephedrone and MDPV) in animal models of addiction, anxiety and depression. A drug discovery focus is directed toward assessing the impact of stereochemistry on designer cathinone pharmacology, as studies are comparing racemic mephedrone with its individual enantiomers. Dr. Rawls' laboratory has shown that the S-enantiomer of mephedrone is relatively inactive and devoid of rewarding properties, but can antagonize anxiogenic effects associated with cocaine and MPDV withdrawal. S-mephedrone may provide a structural and pharmacological template to develop a therapy for psychostimulant addiction. A more recent project by Dr. Rawls is the characterization of the *Mitragyna speciosa* plant, known as "kratom", which contains more than 20 alkaloids, several of which are biologically active. The principal component is mitragynine, which possesses a unique pharmacological profile including opioid- and stimulant-like effects. Dr. Rawls' laboratory has shown that mitragynine displays efficacy against chemotherapy-induced neuropathic pain, and that the effect is dependent on multiple receptors including μ-opioid, α2-adrenoceptors, and GABA. Dr. Rawls also has a long-standing drug addiction K-12 outreach program and curriculum that uses invertebrate flatworms, called planarians, that enables students to study and quantify addiction-related effects in a living animal.

Zachary Wilmer Reichenbach, M.D., Ph.D.

Fellow, Department of Gastroenterology & Hepatology, Temple University Hospital
Adjunct Assistant Professor, CSAR, Lewis Katz School of Medicine

Dr. Reichenbach's early work focused on limiting inflammation in the central nervous system by utilizing different agonists and antagonists of the endogenous cannabinoid system. This work focused mainly on stroke. Studies showed that inhibiting activation of the cannabinoid 1 receptor (CB1R) would limit stroke volume and neurological deficits in a permanent cerebral occlusion model. The role of inflammation in CNS pathology was later extended to also examine its role in contributing to tolerance from chronic opioid usage. Presently, Dr. Reichenbach studies the endocannabinoid system as a means to modulate inflammation and neoplastic processes with a particular interest in pathology of the gastrointestinal tract. Collaborating with Dr. Kelly Whelan from the Department of Pathology and Drs. Ron Tuma and Sara Ward from CSAR, he is

exploring the effect of modulating the cannabinoid system to prevent development and progression of squamous cell cancer of the esophagus. Of particular interest at this time is the effect of blocking the cannabinoid 2 receptor (CB2R) and studying its effect on disease progression. Future studies will also examine efficacy of cannabinoid agents to ameliorate other gastrointestinal pathologies of the esophagus through downregulation of inflammation. Another area of interest involves gastrointestinal motility, and Dr. Reichenbach is studying both the effect of Botox injections in the pylorus to treat gastroparesis, as well as the drug, Eluxadoline, in the treatment of diabetic enteropathy.

Thomas J. Rogers, Ph.D.

Professor, Department of Pharmacology and Fels Institute
Director of Center for Inflammation, Translational and Clinical Lung Research,
Lewis Katz School of Medicine

The basic research interests of the Rogers laboratory have centered on an understanding of the cross-talk between G protein-coupled receptors (GPCRs) at the level of both protein function and gene expression. Dr. Rogers has focused his attention on chemokine and opioid receptors because these groups of receptors play a significant role in the regulation of inflammatory responses. He has been particularly interested in a process termed "heterologous desensitization." This process occurs when one GPCR is activated by its ligand and induces a signaling pathway which leads to the inactivation of a second, and distinct, GPCR. As a part of this process, the GPCRs are able to control the functional activity of a given receptor, and selectively "tune" the inflammatory response by allowing some receptors to have a greater (or lesser) impact on inflammation. For example, the activation of certain chemokine receptors can lead to the inactivation of opioid receptors, and up regulate pain responses. Conversely, the activation of opioid receptors can lead to the desensitization of chemokine receptors such as CCR5. Dr. Rogers has reported that heterologous desensitization of CCR5 inhibits the capacity of CCR5 to act as a co-receptor for HIV, and suppresses the ability of cells to be infected by the virus. The biochemical basis for the cross-talk between GPCRs is an active area of investigation in the Rogers laboratory. They have also become very interested in studying the interactions of tobacco smoke, opiates, and HIV on the development of inflammation in the lungs and brain, because of the frequent abuse of tobacco by intravenous drug users, and the common use of cigarettes by HIV-infected patients. Their work suggests that the combination of these three influences leads to significant changes in the traffic of inflammatory cells into these organs, and the heightened activities of these inflammatory cells is likely to promote the development of chronic inflammation in HIV-positive intravenous drug abusers.

Slava Rom, Ph.D., MBA

Assistant Professor, Department of Pathology and Laboratory Medicine,
Lewis Katz School of Medicine

Dr. Rom's research interests encompass several lines of exploration in the fields of neuroimmunology, neurovirology and neuroinflammation. His ongoing work explores mechanisms of blood-brain barrier (BBB) injury in neuroinflammation and associated immune responses resulting from HIV-1 CNS infection, encephalitis, and cerebral ischemic stroke. In his collaboration with Dr. Yuri Persidsky, he has studied anti-inflammatory, BBB protective, and anti-retroviral effects of cannabinoid receptor 2 (CB2)-selective agonists, inhibitors of poly(ADP-ribose) polymerase (PARP-1), and Glycogen Synthase Kinase 3 (GSK3β) in brain endothelium, macrophages, and peripheral blood leukocytes. In his recent work funded by the National Institute of Neurological Diseases and Stroke (NINDS), he has identified several microRNAs (miRNAs), which exhibit anti-inflammatory characteristics. Overexpression of these miRNAs in an *in vitro*

BBB cellular model, utilizing primary brain microvascular endothelial cells, as well as in an *in vivo* mouse model for encephalitis, resulted in BBB protection and neuroprotection. As a continuation of these findings, Dr. Rom is expanding the potential efficacy of the miRNAs as anti-inflammatory treatments during secondary damage to the CNS following injury by an induced stroke and in a mouse model of multiple sclerosis. The mechanisms by which these miRNAs exert their protective effects is being explored using endothelial cells, microglia and peripheral immune cells, and by measuring alterations in immune mediators including cytokine and chemokine secretion which might affect interaction among these cell types. Another ongoing project is in collaboration with Dr. Scott Rawls, with the aim of investigating epigenetic control of the response to cocaine and designer "bath salts", also known as cathinones.

Bassel Sawaya, Ph.D.

Professor, Department of Neurology & Fels Institute for Cancer Research and Molecular Biology, Lewis Katz School of Medicine

Research in the Sawaya laboratory focuses on central nervous system processes that depend heavily on efficient mitochondrial function, since brain tissue has a high-energy demand. Mutations in mitochondrial DNA (mtDNA), generation or presence of reactive oxygen species (ROS), and environmental factors may contribute to energy failure and lead to neurodegenerative diseases. Many rare metabolic disorders have been associated with mitochondrial dysfunction. Defects in mitochondrial dynamics in patients infected with HIV-1 can lead to neuronal dysfunction that is mainly due to loss of neuronal communication. The relation between mitochondrial dysfunction and the development of HIV-Associated Neurocognitive Disorders (HAND) remains unclear and understudied. HAND has been described to be associated with major learning deficits and impairment of working memory domains. Learning ability and working memory functions are mediated by neurons of the hippocampus, a brain area known to be affected by released HIV-1 proteins, such as Tat, gp120 and Vpr. Hence, the work of the laboratory is to understand the role of HIV-1 proteins in neuronal deregulation through their interplay with the cellular factor, CREB, leading to learning alteration and working memory deficits (premature brain aging). Dr. Sawaya is also interested in understanding the mechanisms used by the viral proteins and by certain cellular factors leading to inhibition of autophagy and eventually loss of spatial and declarative memory.

Stephanie Sillivan, Ph.D.

Assistant Professor, Department of Anatomy & Cell Biology, Lewis Katz School of Medicine

A powerful motivation to seek opioids remains after withdrawal and increases in strength after extended periods of abstinence, suggesting a lasting change in brain function. Perpetual drug-seeking behavior is a direct result of neuroadaptations in the brain that arise from chronic drug exposure and drug tolerance, which represents a huge barrier to full recovery. Unfortunately, knowledge of the cellular mechanisms governing this continued drive is currently very limited. Therefore, a large portion of the research in Dr. Sillivan's laboratory is devoted to identifying molecules and signaling pathways that sustain the motivation for opioid seeking. This work is guided by the hypothesis that continued opioid seeking after prolonged abstinence is supported by unique RNA and protein networks. To accomplish this goal, laboratory members utilize a combination of both molecular biology and behavioral neuroscience to understand mechanisms within the cell that drive maladaptive behaviors. Completion of these studies will hopefully identify new mechanisms of opioid seeking in the drug-free brain, which represents a critical step towards preventing substance use relapse.

Ronald Tuma, Ph.D.

Professor, Department of Physiology, Lewis Katz School of Medicine

The major research efforts in Dr. Tuma's laboratory are directed at investigation of inflammatory reactions that contribute to central nervous system injury following stroke, trauma, and autoimmune disease, and how modulation of the activity of specific cannabinoid receptors influences the progression of these diseases. Experimental models utilized in these investigations include rodent models of stroke, head injury, spinal cord injury and multiple sclerosis (Experimental Autoimmune Encephalitis). His group has demonstrated that modulation of the activation of CB2 receptors has a significant impact on the development of disease in the model of multiple sclerosis, as well as on the magnitude of damage in mouse models of stroke and spinal cord injury, and head injury (in collaboration with a group at Thomas Jefferson University). Currently, Dr. Tuma is investigating the mechanisms by which cannabinoids impact secondary damage to the CNS following injury, including effects on endothelial cells, microglia and peripheral immune cells, and how alterations in cytokine/chemokine release may influence interaction among these cell types. Also, in collaboration with Dr. Ward's laboratory, he is investigating the effects of endogenous cannabinoids, phytocannabinoids and synthetic cannabinoids on the development of neuropathic pain following spinal cord injury.

Ellen M. Unterwald, Ph.D.

Director, Center for Substance Abuse Research

Professor, Department of Pharmacology, Lewis Katz School of Medicine

Dr. Unterwald's research takes a multi-disciplinary approach to study neurobiological mechanisms involved in addictive diseases and related disorders of the central nervous system using pre-clinical rodent models. Her work investigates cellular and molecular adaptations that result from exposure to drugs of abuse including psychostimulants, opiates, nicotine, and alcohol, and how these neuroadaptations drive addiction. One area of interest in the Unterwald laboratory is the identification of cellular mechanisms involved in drug craving and relapse. An important role for the NMDA–GSK3β–mTORC1 pathway in the maintenance of cocaine reward memories has been identified. Dr. Unterwald and her colleagues have demonstrated that disruption of this signaling pathway can erase cocaine-associated contextual memories, thereby abolishing cocaine-seeking behaviors. They are currently testing this therapeutic approach to diminish relapse behaviors to cocaine self-administration in a rat model. Another area of interest in the Unterwald laboratory involves neuroimmune interactions in the setting of psychostimulant exposure. In collaboration with Dr. Rawls, the regulation of chemokines during self-administration of cocaine and the synthetic cathinone, MDPV, is under investigation, along with the impact of the chemokine system on addiction-related behaviors. Their work has demonstrated that a CXCL4 receptor antagonist can attenuate psychostimulant reward, reinforcement and relapse. The Unterwald laboratory also studies the role of stress systems on cocaine withdrawal and reinstatement, and the mechanism of increased susceptibility to substance abuse in the presence of post-traumatic stress disorder (PTSD). Results from these studies provide important information about the cellular and molecular mechanisms underlying addiction-relevant behaviors, and point to novel potential therapeutic targets to prevent or treat substance use disorders.

Ellen Walker, Ph.D.

Professor and Chair, Department of Pharmaceutical Sciences, School of Pharmacy

Dr. Walker's research program examines the pharmacological and behavioral basis underlying the preclinical effects of stimulants, opioid analgesics, novel nootropics (drugs which are cognitive enhancers), and cancer chemotherapeutics. Most of the projects in the laboratory examine the role of drugs on various motivated behaviors. The rise in non-medical use of prescription opioids has left clinicians with the dilemma of how to treat pain, while at the same time reducing the potential for opioid abuse. Dr. Walker studies whether the occurrence of pain, and the type of pain treatment, protects or predisposes the subject to the reinforcing effects of prescription opioids. Her rodent models use a variety of behavioral tasks such as

progressive ratio procedures, operant self-administration, conditioned place preference, reinstatement, extinction, and drug discrimination. Another key project addresses the public health concern that novel psychoactive substances have appeared on the illicit market without pharmacological characterization and/or understanding of the behavioral consequences of repeated use. Dr. Walker's laboratory is examining the subjective and reinforcing effects of such compounds, including mephedrone, a component of "bath salts", and the analgesic and subjective effects of novel synthetic opioids to determine the relative risk of abuse liability for these agents, and to provide potential strategies to manage such abuse. Finally, Dr. Walker's laboratory also examines a number of compounds from various pharmacological classes for their capacity to either improve or disrupt memory processes.

Sara J. Ward, Ph.D.

Assistant Professor, Department of Pharmacology, Lewis Katz School of Medicine

Dr. Ward's research focuses on the behavioral, pharmacological and anti-inflammatory effects of cannabinoid-based compounds on CNS injury and disease using pre-clinical rodent models. Her work investigates the safety and efficacy of plant-based and synthetic cannabinoids in rodent models of neuropathic pain, spinal cord and brain injury, ischemia, and substance abuse. One area of interest is the identification of synergistic or sub-additive effects of two different cannabinoids or cannabinoid/opioid interactions on pain and inflammation. The Ward laboratory was the first to demonstrate that the plant-based cannabinoid, cannabidiol (CBD) is effective at preventing neuropathic pain in a mouse model of chemotherapy-induced peripheral neuropathy, and follow-up studies showed robust synergistic interactions in this model with combinations of CBD and Δ^9-tetrahydrocannabinol (THC). These findings have led to collaboration with Lankenau Medical Center to initiate clinical trials for a hemp-derived CBD-rich extract in a patient population. In collaboration with Dr. Ronald Tuma, she is also studying the protective effects of plant-based and synthetic cannabinoids, as well as interactions between opioids and ethanol on traumatic spinal cord injury and brain injury. Results from these studies are providing important information about the potential effectiveness and mechanisms associated with cannabinoid-based treatment strategies to mitigate CNS injury and associated substance use disorders.

Mathieu Wimmer, Ph.D.

Assistant Professor, Department of Psychology & Program in Neuroscience, College of Liberal Arts

Dr. Wimmer's laboratory combines animal models of addiction with molecular biological techniques to study epigenetic mechanisms underlying addiction susceptibility. Drug addiction is a massive public health concern that inflicts extensive burdens on our economy and society. The etiology of drug abuse has a large genetic component and epidemiological studies suggest that addiction is heritable. However, efforts to identify the genes predictive of addiction vulnerability have yielded a few candidates that thus far failed to improve therapeutic approaches to treat substance use disorder. The emergence of epigenetic studies has provided a concrete mechanism for the long-held idea that psychiatric diseases are caused by complex interactions between environmental and genetic factors. Dr. Wimmer has established a highly translational paradigm of paternal opioid drug taking, using morphine self-administration in rats to study the influence of drug exposure on future generations. The Wimmer laboratory is interested in two major questions: (1) How is the information passed on from fathers to their offspring? How can paternal drug taking alter the germline epigenome (sperm)? Which germline epigenetic reprogramming events are critical for shaping development toward addiction vulnerability in the next generation? (2) What has changed in the brain of the offspring produced by drug-treated fathers? What are the functionally relevant neuro-epigenetic processes that increase addiction-like behavior in the first generation progeny? Dr. Wimmer and his research team utilize a combination of behavioral animal models of addiction, molecular biology and gene-targeted epigenetic editing tools to delineate the mechanisms that contribute to addiction vulnerability and resilience.

CSAR Research Highlights 2017-2019

Overview

The Center for Substance Abuse Research (CSAR) brings together a group of premier researchers dedicated to investigating fundamental questions regarding how drugs of abuse affect neural pathways and other important processes including immune and endocrine function. Knowledge gained from these studies has led to the identification of potential novel targets to reduce drug-seeking behaviors. The studies described in this section of the Report are examples of the breadth and depth of the research ongoing in CSAR. CSAR brings multi-dimensional approaches, ranging from molecular to biochemical, cellular, and behavioral, to address a wide spectrum of questions about drugs of abuse that will lead to a better understanding of the biological basis of addictive diseases. Investigators in the Center are working on a spectrum of substances, including opioids, cannabinoids, stimulants (eg, cocaine, "bath salt" synthetic cathinones, methamphetamine), alcohol and nicotine. The research is elucidating neuronal circuits impacted by drugs of abuse that contribute to the development and maintenance of addiction, identifying potential targets for therapies for substance use disorders, dissecting genetic factors that impact susceptibility or resilience to substance abuse and dependence, studying alterations in neuropeptide, neurotransmitter, cytokine and chemokine systems induced by drugs of abuse, and uncovering interactions between the neural and immune systems that potentially contribute to, or are a consequence of, intake of these substances. Ongoing research seeks to understand the interaction of drugs of abuse with HIV infection. Pain, mood disorders and stress are motivators for many people to begin using drugs that can lead to addiction. Ongoing studies in CSAR are looking for alternative treatments for pain that are opioid-sparing, by examining combination therapies that would allow reduced doses of opioids or by testing non-opioid agents. Several of the important research projects undertaken by CSAR faculty address the intersection of substance abuse with various mood disorders as they relate to drug seeking, relapse, anxiety and depression. CSAR is an incubator that is empowering novel collaborations and avenues of investigation to understand the biological basis of a major medical and societal problem, drug abuse.

Interaction of Opioids, Cannabinoids, and Psychostimulants with the Immune System: Implications for Pain, Inflammation and Addiction

Overuse of opioids is currently a major problem of epidemic proportion, with 47,600 deaths in the United States in 2017. According to a 2017 report from the Substance Abuse and Mental Health Services Administration (SAMHSA), 63% of people who misused opioids gave relief of pain as the major reason for taking the drugs. It is estimated that 30% of Americans suffer from chronic pain. Investigators in CSAR are following several lines of investigation that would reduce the doses of opioids needed for effective analgesia, and thus their potential to produce dependence. One of the strategies being pursued by CSAR researchers involves using compounds which block a class of inflammatory molecules, chemokines, in conjunction with low doses of opioids. Interest in cannabinoids has been renewed in the last few years as 33 states have legalized marijuana for medical purposes. The conditions specified as legitimate to qualify

for medical marijuana vary between states and include a long list of ailments that produce pain, as well as autoimmune diseases that have an inflammatory component, such as multiple sclerosis and inflammatory bowel disease, and a variety of other conditions spanning autism, epilepsy, seizures, spasticity, glaucoma, and HIV. The evaluation of marijuana and its components for beneficial effects has a surprisingly small literature, even though the plant and its components are widely touted as having medicinal properties. CSAR investigators are exploring analgesic effects of components of the marijuana plant other than Δ^9-tetrahydrocannabinol (Δ^9-THC), including cannabidiol (CBD), as well as synthetic compounds that bind to the classical cannabinoid receptors or activate newly recognized cannabinoid receptors, GPR18 and GPR55, involved in pain pathways. One approach being explored by CSAR laboratories is to utilize combinations of low dose opioids and cannabinoids for pain relief, which would reduce the potential of drug dependence during pain treatment.

As early as 2002, CSAR investigators showed that infusion of an opioid directly into the pain-sensing periaqueductal gray (PAG) region of the brain produced a robust analgesic response. Infusion of selected chemokines, molecules that mediate cell signals and inflammation in the immune system, prior to morphine administration blocked morphine-induced analgesia. Electrophysiological recordings of PAG neurons demonstrated that chemokines could dampen morphine's effect on neuronal activity. It was also shown that single neurons of the PAG express both chemokine receptors and opioid receptors, and that cells transfected with the mu opioid receptor (the receptor through which morphine produces its effects) and a chemokine receptor can form heterodimers. This intimate interaction between these two classes of G protein-coupled receptors (GPCRs) is called "heterologous desensitization". These studies provided a mechanism to explain why, in many pain conditions, opioids have diminished potency. If chemokines are released as part of an inflammatory process that accompanies the insult that generates the pain, then these inflammatory mediators could desensitize opioid receptors, making them less responsive to morphine. Based on these observations, the hypothesis was formulated that chemokine receptor antagonists, by blocking the signaling ability of chemokines at their receptors, would augment opioid potency and provide greater analgesia for a given dose of an opioid. Studies carried out by Drs. Adler, Cowan, Eisenstein and Rawls found that combining one or more chemokine receptor antagonists with a sub-maximal dose of morphine shifted the morphine dose-response curve to the left in several rodent pain models. The effect was not selective for morphine, as significant shifts in opioid dose-response curves were also observed for oxycodone and meperidine. These findings present a new paradigm for reduction of opioid dosing that involves blocking a class of molecules associated with inflammation that is frequently released in painful conditions.

Chemokine receptor antagonists enhance the analgesic potency of morphine. The combination is "opioid sparing", giving maximal relief with lower doses of the opioid.

Examination of chemokines in the CNS has been extended by Drs. Unterwald and Rawls who are investigating the potential role of the CXCR4/CXCL12 chemokine system in the actions of psychostimulants. The CXCR4 receptors for the chemokine CXCL12 are found on neurons in several areas of the brain, and their activation can modulate neuronal activity. Drs. Unterwald and Rawls have shown that a CXCR4 antagonist, AMD3100, can attenuate the reinforcing effects of cocaine and the synthetic cathinone, MDPV, thus reducing drug-seeking behaviors in a rat model of iv drug self-administration. Further, CXCL12 can enhance the locomotor-activating effects of cocaine. This novel line of investigation strongly implicates chemokines as important modulators of mesolimbic dopamine transmission and as contributors to drug-seeking behaviors for psychostimulants.

It has been suggested, based on epidemiologic data, that legalization of marijuana reduces use of opioids, although there is at least one contradictory report. To investigate this premise, a strategy that has been pursued by CSAR investigators to control pain is to use combinations of cannabinoids with low doses of opioids. Drs. Eisenstein, Adler, Cowan, Tallarida and Rawls collaborated on a study testing the efficacy of morphine in combination with two synthetic cannabinoids in two rodent pain assays. It was found that WIN55-212, a synthetic cannabinoid that binds to both cannabinoid receptors, CB1 and CB2 receptors, synergized with morphine in providing analgesia more effectively than that achieved with morphine alone. Using selective CB1 and CB2 receptor antagonists, the analgesic activity of the opioid/WIN combination was shown to be mediated via the CB1 receptor. In another test, an additive effect of low doses of morphine plus a selective CB2 receptor agonist was observed in rats. These studies provide evidence that combinations of cannabinoids and opioids might be another approach to reducing the doses of opioids needed for adequate pain relief.

Drs. Ward and Tuma are testing the anti-inflammatory effects of the phytocannabinoid, cannabidiol (CBD). CBD is one of the hundreds of different molecules in the marijuana plant. It is not psychoactive and does not bind to either of the traditional cannabinoid receptors (CB1 or CB2), but it is reported to have beneficial activities for a number of conditions that involve pain and inflammation. These CSAR investigators used a mouse model of spinal cord injury and measured development of pain by increased thermal sensitivity in the paw. They found that mice treated with CBD following spinal cord injury had reduced thermal sensitivity and also decreased T cell infiltration into the injured site. CBD did not impair spatial learning and memory, nor did it produce physical dependence as assessed by precipitated withdrawal. Drs. Ward, Tuma, Tallarida, and Walker used a mouse model of chronic neuropathic pain induced by the chemotherapeutic agent, paclitaxel, and found that either Δ^9-THC or CBD provided effective analgesia. Importantly, the combination of low, ineffective doses of either CBD or Δ^9-THC were synergistic when given together. These results provide an explanation for why marijuana, which contains both CBD and Δ^9-THC, is claimed by patients to provide greater pain relief than that of purified Δ^9-THC alone.

Two compounds found in the marijuana plant, cannabidiol and Δ^9-THC, synergize in relieving neuropathic pain.

Dr. Rawls is exploring potential beneficial properties and abuse liability of mitragynine, one of the biologically active alkaloids found in kratom, which comes from the tree, *Mitragyna speciosai.* Kratom is used extensively in southeast Asia in traditional medicine to treat pain and manage opioid withdrawal. It has been shown to have activity at opioid receptors and is claimed to be an analgesic, but also to have stimulant properties. New evidence from the Rawls laboratory indicates that mitragynine is efficacious against oxaliplatin-induced neuropathic pain in male and female mice. Its antinociceptive effects are blocked by antagonism of mu opioid receptors or alpha$_1$- and alpha$_2$-adrenoceptors. Ongoing studies are directed towards identifying spinal and supraspinal mechanisms underlying the antinociceptive effects of mitragynine, and to characterize mitragynine in animal models of addiction.

Dr. Abood's laboratory is studying what have been termed "orphan" cannabinoid receptors. Two of these GPCR receptors, GPR55 and GPR18, were identified by homology screening, and at the time they were discovered, their endogenous ligands were not known. Interest in these receptors has grown as they have been implicated in inflammatory and neuropathic pain, metabolic disorders, and other pathologies. Her laboratory has carried out high-throughput screens for agonists and antagonists at these receptors using the NIH library of 300,000 compounds. Lysophosphatidyl inositol (LPI) was identified as an endogenous agonist for GPR55 and shown to mediate pain responses. ML184 was identified as a synthetic agonist at this receptor. Given the need for alternatives to opioids, one approach to enhanced analgesia could be to develop antagonists at GPR55. To this end, Dr. Abood's laboratory has carried out structural studies on the GPR55 receptor to identify the amino acids that mediate binding of LPI and induce signaling by the receptor. Through the use of molecular models and site-directed mutagenesis, amino acid residues were identified that are part of the orthostatic binding pocket, and others that are crucial for GPR55 signaling. The goal of this research is to use this structural information to synthesize high-affinity ligands for this receptor. GPR18 is of interest because it has been associated with pain, inflammation, cancer and other conditions. Dr. Abood carried out collaborative research to test derivatives of a parent benzothiazole compound, identified in the screen mentioned above, as candidate antagonists at this receptor. There is potential for these newly discovered cannabinoid receptors and their ligands, which are devoid of addictive properties, for treatment of pain and potentially other disorders. In related studies, Dr. Persidsky's laboratory has had an abiding interest in the integrity of the blood-brain barrier (BBB), as its disruption allows inflammatory cells to enter the brain and also is a portal of entry for HIV carried by inflowing leukocytes. He has shown that GPR55 agonists protect the tight junctions of the BBB from opening during inflammation. More recently, Dr. Persidsky has published results showing that activation of GPR55 increases neural stem cell proliferation and hippocampal neurogenesis. These lines of scientific inquiry are of significance because they are providing novel information about the importance of the expanding endocannabinoid system in a variety of physiological processes.

Newly identified putative cannabinoid receptors, GPR55 and GPR18, may have a role in pain perception.

Neural Pathways and Addiction Behaviors

It is well accepted that conditioned learning plays a large role in the development of addictive behaviors. Of particular importance in treating substance use disorder is the prevention of relapse. Exposure to cues previously associated with cocaine availability can lead to a conditioned physiological response accompanied by intense drug craving and relapse to drug-seeking behaviors. One goal of addiction treatment is to extinguish previously learned associations between the positive subjective effects of cocaine and environmental cues signaling cocaine availability. Dr. Unterwald's laboratory has made a major advance in our knowledge about molecular mechanisms involved in the maintenance of cocaine-associated memories. Her studies have demonstrated that the Akt/GSK3β/mTORC1 signaling pathway in the hippocampus, nucleus accumbens, and prefrontal cortex is

A signaling pathway engaged by reactivation of cocaine reward memories, GSK3β/mTOR, is a potential target for preventing cocaine relapse.

engaged by reactivation of cocaine reward memories, and that inhibition of GSK3β after reactivation of these memories interferes with memory reconsolidation and prevents later cocaine-seeking activity. To further explore the role of this pathway in cocaine reward, she has used site-directed viral Cre delivery (AAV-Cre-GFP) to GSK3β-floxed mice to generate a mouse line with conditional deletion of GSK3β in the nucleus accumbens. These studies demonstrated that activation of GSK3β in the nucleus accumbens is necessary for the rewarding effects of cocaine, but not morphine. As the GSK3β signaling pathway appears to be critical for induction of cocaine reward and also for reconsolidation and maintenance of cocaine-associated contextual memories, it may be a promising target for treatment of cocaine use disorder.

A growing body of research indicates that insults experienced by parents, which modify gene expression that do not change the DNA sequence in the genome, can be inherited by their offspring. Epigenetic inheritance refers to the mechanisms by which changes in non-germline information are transmitted from parents to their offspring independent of DNA mutation.

Dr. Wimmer has been utilizing a multigenerational rat model of paternal drug taking to study the epigenetic reprogramming associated with addiction susceptibility. Dr. Wimmer's laboratory team has shown that adult male, but not female, offspring of morphine-exposed sires (fathers) self-administer more morphine and work harder to earn infusions of morphine than control-sired offspring. These effects were specific to morphine, since opioid sire exposure did not impact the self-administration of sucrose or cocaine. Paternal morphine exposure also disrupted object memory in female, but not male offspring. Collectively, this research is adding to the small but mounting evidence suggesting that parental experience can result in specific alterations in the physiology and behavior of addiction susceptibility of the future progeny.

Male rats taking morphine have offspring that will work harder to earn infusions of the opioid, an example of epigenetic influences on addiction susceptibility.

Kappa opioid receptors (KOPR) are involved in many physiological processes and psychological states that include addiction, itch, analgesia and depression. Dr. Liu-Chen's laboratory was one of the first to clone the kappa opioid receptor, and she has continued her studies into the potential clinical utility of kappa receptor agonists and antagonists. In collaboration with Dr. Mann at the Max Planck Institute at Matinsreid, Germany, high-throughput phosphoproteomics was used to investigate signaling induced by structurally diverse kappa receptor agonists. Quantification of 50,000 different phosphosites provided a system's view of KOPR *in vivo* signaling in mouse brain, revealing novel mechanisms of drug action. In particular, the mammalian target of rapamycin (mTOR) pathway was activated by U50,488H, a KOPR agonist causing aversion, a typical KOPR-mediated side effect, but not by drugs that were not aversive, such as HS666 and 5'-GNTI. Inhibition of mTOR during KOPR activation abolished aversion, while preserving beneficial antinociceptive and anticonvulsant effects. These results established high-throughput phosphoproteomics as a general strategy to investigate GPCR *in vivo* signaling, enabling prediction and modulation of behavioral outcomes, as well as elucidating potential targets for development of GPCR therapeutics with fewer side effects.

Purinergic P2X7 receptors are located on neurons, astrocytes and microglia, and P2X7 activation can result

in the release of glutamate, dopamine, cytokines, and chemokines which have known interactions with psychostimulant drugs. Drs. Potula and Rawls tested the role of these receptors on the effects of methamphetamine and the synthetic cathinone, MDPV. They found that the P2X7 antagonist, A438079, dose-dependently inhibited the facilitation of intracranial self-stimulation produced by both psychostimulants, indicating that P2X7 receptor activation is important for stimulant-induced reward. However, A438079 did not alter dopamine levels in the nucleus accumbens evoked by methamphetamine, suggesting that the inhibitor must work through a dopamine-independent mechanism.

Exposure to stressful life events is associated with increased susceptibility to substance use disorders, as well as mood disorders. Further, stress can be a potent stimulus for relapse in persons recovering from a substance use disorder. Dr. Briand, in the Department of Psychology at Temple, investigated the effect of adolescent isolation stress in male and female mice, and found that isolation increased cocaine seeking in both sexes. Mechanistically, stress produced presynaptic alterations in glutamatergic transmission in the nucleus accumbens in both sexes, as assessed by whole-cell recordings. Dr. Kirby's laboratory has a long-standing interest in the effects of stress on the serotonin system and its relation to drug-seeking behaviors. Serotonin levels contribute to mood, depression, and anxiety. Dr. Kirby has been testing the hypothesis that repeated opioid exposure dysregulates the serotonin system and responses to stress, creating a negative mood state that motivates relapse as a form of "self-medication". Dr. Kirby has shown that serotonin neurons in the dorsal raphe nucleus from animals exposed to stress-induced opiate relapse had an increase in GABAergic inhibitory postsynaptic current (IPSC) amplitude, indicating sensitization of inhibitory GABA receptors on serotonin neurons. This neuroadaptation creates a hypo-serotonergic state, negative mood, and potentially increased relapse vulnerability. Current studies are using genetically engineered mice which lack GABA-A receptors specifically on serotonin neurons to test the hypothesis that their stress-induced relapse potential will be reduced. Dr. Kirby will also use excitatory or inhibitory Cre-dependent Designer Receptor Exclusively Activated by Designer Drugs (DREADDs) in tryptophan hydrolase 2-Cre (Tph2-Cre) rats to examine the impact of manipulating serotonin dorsal raphe nucleus (DRN) neuronal activity *in vivo* on heroin self-administration and stress-induced reinstatement.

Dysregulated glutamate and serotonin pathways contribute to cocaine and heroin relapse.

Several other investigators in CSAR are also exploring stress and its relationship to substance abuse. Dr. Bangasser is particularly interested in sex differences in activation of stress responses, which have been suggested to translate into sex differences in drug-seeking behaviors in humans. She has found sex differences in circuits activated by corticotropin releasing factor in rats that may help explain why females are more sensitive to stressors than males. Dr. Unterwald's laboratory has examined expression levels of a co-chaperone of the glucocorticoid receptor, FKBP5 (FK506 binding protein 5) in male and female rats maintained on chronic cocaine. Chronic administration of cocaine significantly elevated FKBP5 mRNA in the bed nucleus of the stria terminalis and the paraventricular nucleus of the hypothalamus in both sexes, suggesting a novel mechanism for the dysregulation of the stress axis by cocaine. The laboratory of Dr. Sillivan is investigating microRNAs (miRNAs) and their regulation of gene expression. She has shown that

specific miRNAs regulate persistent stress-enhanced memories. She also carried out a bioinformatics analysis of long-lasting changes in miRNA-mediated pathways in the amygdala following acute stress and stress-enhanced fear learning, a strategy she is currently employing to investigate perseverant drug-seeking behaviors in opioid addiction.

There is evidence from the clinical literature that traumatic brain injury (TBI) is causally related to substance abuse. The military is particularly interested in this association. Several researchers in CSAR are using rodent models of TBI and investigating the effect of this type of injury on the effects of drugs of abuse. Drs. Ramirez and Rawls have found that male mice that experienced a TBI during adolescence show greater rewarding effects of cocaine than control mice. These mice have altered dendritic spine morphology and reduced levels of dopamine in the nucleus accumbens after TBI. Dopamine is associated with pleasurable and rewarding feelings and is elevated by cocaine which could explain why individuals who suffered a TBI might turn to this drug to compensate for a hypodopaminergic state.

Identifying Potential Therapeutic Targets for Substance Use Disorders

Several of the project descriptions above bear on pathways engaged by drugs of abuse and so also have implications for therapeutic interventions (e.g., projects on chemokines and cocaine, on GSK3β and cocaine reward, and on development of new agonists and antagonists at GPR55 and GPR35 cannabinoid receptors). A few other areas of investigation that are leading to development of therapeutics for substance abuse are described below.

Dr. Muschamp has a long-standing interest in the role of the neuropeptide orexin/hypocretin in goal-directed behaviors including cocaine-seeking. He discovered that suvorexant, an orexin receptor antagonist, reduced motivation for cocaine in a rat model of iv drug self-administration. In collaboration with Dr. Rawls, he found that self-administration of the synthetic cathinone, MDPV, was also attenuated by suvorexant under certain, but not all, self-administration conditions. Concurrent with self-administration sessions, 50 kHz ultrasonic vocalizations (USVs) were recorded as a measure of a positive hedonic state. These USVs were high during anticipation of drug self-administration and during the early drug load-up period. Suvorexant significantly reduced 50 kHz USVs in rats trained to self-administer either cocaine or MDPV. These data suggest that suvorexant could be a useful therapeutic for stimulant use disorder.

A compound used in Chinese herbal medicine, (-)-stepholidine, blocks reinstatement of self-administration of the cathinone, MDPV.

There are currently no FDA-approved medications for treatment of cocaine use disorder. Dr. Rawls has been investigating the role of glutamate transmission in the actions of cocaine. One viable therapeutic target within the glutamate system is the glutamate transporter subtype-1 (GLT-1), an astrocytic protein that clears extracellular glutamate. GLT-1 transport mechanisms are dysregulated during cocaine exposure and contribute to enhanced glutamate transmission in brain regions involved in drug-seeking behaviors. Using preclinical models of drug self-administration, Dr. Rawls has extensively investigated drugs which activate

GLT-1 transporters, including ceftriaxone and clavulanic acid, as possible therapeutics for cocaine addiction with promising results. Based on findings from these preclinical studies, Dr. Mary Morrison has carried out a phase I clinical trial on clavulanic acid in persons with cocaine use disorder. Positive results have led to pursuing further clinical studies with this compound to test the efficacy of clavulanic acid for cocaine use disorder. A newer line of investigation is utilizing another GLT-1 activator, troriluzole. Dr. Rawls' laboratory has shown that troriluzole reduces reinstatement to cocaine-seeking in rats induced by cues previously associated with cocaine self-administration, and also reduces locomotor sensitization produced by repeated cocaine administration. Troriluzole efficacy extends to opioids as well, with results showing that troriluzole reduces oxycodone intake and reinforcement in rat models of self-administration.

Clavulanic acid and troriluzole both reduce glutamate transmission. Clavulanic acid is in human trials for cocaine use disorder.

Dr. Liu-Chen characterized the pharmacological profile of (-)-stepholidine, which is an alkaloid from a Chinese herb that has been shown to attenuate the reinforcing effects of heroin. Work from her laboratory has shown that (-)-stepholidine is a dopamine D1 receptor agonist/D2 receptor antagonist. Working together with Dr. Rawls, she tested the hypothesis that stepholidine would be effective in reducing reinstatement to the cathinone, MDPV. It was found that stepholidine dose-dependently reduced cue and drug-primed reinstatement of MDPV-seeking behaviors in the rat. These results suggest potential utility for this compound in preventing relapse to MDPV or other psychostimulant use.

Drugs of Abuse and HIV

Dr. Ramirez investigated the effect of methamphetamine on production of brain endothelial-derived extracellular vesicles (EVs) in the plasma of HIV-infected humanized NSG mice. The mice were followed longitudinally for 104 days and showed persistent HIV viremia, as well as a decline of CD4 T cells, verifying the utility of this HIV animal model. Methamphetamine administration increased production of occludin-carrying EVs in HIV-1-infected mice. Using the same animals, Dr. Raghava Potula found that HIV-1-infected humanized mice exposed to methamphetamine have increased expression of the immune-inhibitory programmed cell death-1 (PD-1) marker in CD4+ and CD8+ T cells and downregulated interferon-γ production, suggesting a bias towards an immunosuppressive phenotype.

Dr. Eugen Brailoiu studied the effects of the HIV-1 Tat protein on the activity of neurons from the nucleus accumbens in the presence of cocaine. Clinical data suggests that HIV-1 neuropathology is more severe in HIV-1+ patients who use cocaine. Dr. Brailoiu showed that HIV-Tat triggers a Ca^{2+} signaling cascade in medium spiny neurons of the nucleus accumbens, leading to neuronal depolarization. Further, cocaine produced a dose-dependent potentiation of the effect of Tat on cytosolic Ca^{2+}. These results suggest an interaction between products of HIV and cocaine on neurons of the accumbens, which may be relevant for the reward axis in patients who are HIV-1-positive and abuse cocaine.

The laboratory of Dr. Yuri Persidsky has been investigating the putative cannabinoid receptor, GPR55, as

an important mediator of anti-inflammatory events in the brain. He has shown that GPR55 is vital in maintaining the integrity of the blood-brain barrier. In a project carried out using GPR55 knockout mice bred in the CSAR P30 Animal Core, he verified that GPR55 agonists were protective in wild-type, but not GPR55 null mice, against neuroinflammation induced by HIV-Tat and the HIV gp120 molecules.

Dr. Rogers, in a collaborative study with Dr. Jay Rappaport, investigated the effects of chronic morphine on Simian Immunodeficiency Virus (SIV) infection in rhesus macaques. Work in Dr. Rogers laboratory showed that chronic morphine treatment elevated the numbers of circulating T regulatory (Treg) cells, and induced the functional activity of Th17 cells in the blood. In addition, chronic morphine treatment increased the numbers of circulating T cells which express gut-homing receptors (CD161 and CCR6), and augmented the numbers of T cells which express receptors that are important for HIV infection (CCR5 and beta7 integrin). These results show that chronic morphine administration is likely to act to increase susceptibility of T cells to infection, and at the same time to boost the traffic of T cells to the gut (a critical aspect of HIV infection). They also found that the numbers of circulating plasmacytoid dendritic cells are significantly increased in SIV-infected animals receiving morphine treatment. Plasmacytoid dendritic cells are potent inducers of Treg cell activity, and this may explain the increased numbers of Treg cells following morphine treatment.

In monkeys infected with SIV, morphine exposure increases susceptibility of T cells to infection.

Finally, Drs. Rogers and Persidsky are examining the effect of combinations of tobacco smoke, morphine and HIV on inflammatory responses in the lungs and brains of humanized mice that are HIV-infected. The results from experiments with humanized mice infected with HIV show that the combination of smoke and morphine has adverse effects on CD4/CD8 ratios in the periphery, elevates levels of circulating pro-inflammatory cytokines, and significantly induces microglial cell activation in the brain. These results are particularly important given the frequent use of tobacco products by persons with opioid use disorder.

Summary

Investigators in CSAR are taking a wide variety of approaches to dissecting the fundamental questions of what motivates addictive behaviors, the brain circuits and molecules controlling these behaviors, and identification of potential therapeutic targets to block or interrupt these pathological behaviors. There is an impressive spectrum of drugs of abuse under investigation, which is allowing delineation of processes that are unique to one substance and those that are shared by several classes of abused drugs. Several projects are testing how concomitant exposure to drugs of abuse and HIV or its products alters addictive behaviors or influences the course of HIV infection and neuropathology. Basic discoveries emanating from this research are elucidating previously unknown interconnections between the neural and the immune systems that modulate addictive processes and are important in pain. The interdisciplinary approaches used by members of CSAR continue to lead to novel insights into the fundamental processes that control substance abuse.

CSAR Faculty Activities and Honors

Mary Abood

Member, Program Committee, International Cannabinoid Research Society, 2017- 2019
Member, IUPHAR Receptor Nomenclature Committee for Cannabinoid Receptors
Member, Editorial Board, *Cannabis and Cannabinoid Research*, 2016-present
Ad-Hoc Reviewer, ZDA1-GXM-A-01/02, NIDA Centers P50 and P30 review committees, 2018, 2019
Ad-Hoc Reviewer, ZRG1 MDCN-R 86 – AREA/R15, 2017-2019
Member, Temple University IACUC
Member, LKSOM Committee on Tenure
Member, BMSC Admission Committee
Member, Dean's Committee on Non-Tenure Track Faculty Promotion Guidelines Taskforce, LKSOM
Member, Dean's Advisory Committee
Member, Medical Faculty Senate Research Committee
Member, Anatomy and Cell Biology Tenure and Promotion Committee
Co-Chair, CSAR Equipment Committee
Member, CSAR Appointment, Tenure and Promotion Committee
Member, CSAR Faculty Search Committee 2017-2018
Member, Internal Advisory Committee, NIDA T32 Institutional Training Grant

Martin Adler

Member, Editorial Board, *Journal of Neuroimmune Pharmacology*, 2006-present

Debra Bangasser

Director, College of Liberal Arts Program in Neuroscience: Systems, Behavior, and Plasticity, Temple University, Philadelphia, PA 2019–Present
Associate Director, Master's Program in Neuroscience: Systems, Behavior, and Plasticity, 2016–2019
Grant reviewer, NSF, Ad Hoc, BIO/IOS, Neural Systems 2018
Grant reviewer, NIH, Behavioral Neuroscience Fellowship (F31, F32) Study Section F02A) 2018
Chair, Neuroscience Undergraduate Committee, Neuroscience Program 2018- Present
Member, Neuroscience Planning Committee 2016-2017
Member, Diamond Research Award, Selection Committee 2019
USA Councilor, International Behavioral Neuroscience Society 2019–Present
Member, Diversity Statement Committee, International Behavioral Neuroscience Society 2018–Present
Member, Trainee Award Committee, Society for Neuroscience, 2018–Present
Member, Program Committee, Philadelphia Chapter of the Society for Neuroscience, 2018
Member, Animal Research Committee, American College of Neuropsychopharmacology 2018–Present
Web Editor, American College of Neuropsychopharmacology, 2018–Present
Member, Operations Committee, Psychology Department 2016–Present
Member, Strategic Planning Committee, College of Liberal Arts, 2016–Present
Co-Chair, Education Working Group, College of Liberal Arts 2016-2017

Councilor, Philadelphia Chapter of the Society for Neuroscience, Philadelphia, PA 2015–Present
Member, Minority Task Force, American College of Neuropsychopharmacology 2015–2019

Mary Barbe

Session Chair, International Ergonomics Association, 2018
Session Chair, Orthopaedic Research Society, 2019
Session Chair and Proceedings paper reviewer, Human Factors and Ergonomics Society, 2017-2018
Board Member, Advances in Mineral Metabolism 2017-2019; Vice President 2019
Member, Editorial Board, *BMC Musculoskeletal Disorders*
Senior Editorial Board Member, *Scientific Reports*, *Nature Research*
Ad-Hoc Reviewer, Extramural Medical Research, Military Operational Med, 2018
Ad-Hoc Reviewer, ZRG1 SBIB-Y (30) I - Instrumentation: Biomedical Imaging
Ad-Hoc Reviewer, Alzheimer's and Related Diseases Research Award Fund, Virginia Commonwealth University, 2018
Ad-Hoc Reviewer, Stryker Orthopaedic Research Society, Women's Research Fellowship Award, 2017-2019
Ad-Hoc Reviewer, ZAT1 AJT (07) 1, and 2019/08 ZAT1 JM (01) 1, 2018-2019
Ad-Hoc Reviewer, European Science Foundation– Science connect Peer Review Services, Research Foundation Flanders (FWO), 2019
Member, Faculty Search Committee, Anatomy and Cell Biology Department, 2017
Member, Search Committee for Director of ULAR, 2019
Member, Faculty Search Committee for Director of Fels Cancer Institute, 2019
Member, Faculty Search Committee, College of Engineering, 2017, 2019
Chair, Anatomy & Cell Biology Department, Appointments & Promotions Committee 2017-2019
Member, Promotion and Tenure Committee, College of Engineering, 2017
Associate Chair of Research, Anatomy and Cell Biology Department, 2017-2019
Research mentor, Step-Up Program for minorities, 2018

James E. Barrett

Editor-in-Chief, *Handbook of Experimental Pharmacology*
Treasurer, International Union of Basic and Clinical Pharmacology (IUPHAR)
Member, Congressionally Directed Medical Research Program, Department of Defense on Non-Opioid Pain Management, Chronic Migraine, and Post-Traumatic Headache Translational Science Award, Bench Testing, Therapeutic/Indication Pairing Strategies
Expert Reviewer, European Union Innovative Medicines Initiative (IMI) – Autism Spectrum Disorders
Chair, Medical Research Program of the Congressionally Directed Medical Research Program – Pain
Chair, National Center for Advancing Translational Sciences – CTSA Network – Trial Innovation Centers (TICs)
Chair, NIDA Translational Avant-Garde Award for Development of Medication to Treat Substance Use Disorders
Member, Clinical and Translational Science Award Collaborative Innovation Award Special Emphasis Panel
Chair, National Institute on Drug Abuse Special Emphasis Panel – "Development of medications to prevent and treat opioid use disorders and overdose".
Member, National Institute on Drug Abuse Special Emphasis Panel, NIDA Research Education Program for Clinical Researchers and Clinicians.

Member, National Institute on Drug Abuse, Special Emphasis Panel. "HEALing Communities Study: Developing and Testing an Integrated Approach to Address the Opioid Crisis"
Chair, "Development of Medications to prevent and treat opioid use disorders and overdose"
Chair, Special Emphasis Panel for NIDA Medications Development
Chair, Laboratories for early clinical evaluation of pharmacotherapies for substance use disorders
Member, Editorial Advisory Board, Technology Transfer and Entrepreneurship
Emeritus Professor, Drexel University College of Medicine

Lisa Briand

Associate Director, Master's Program in Neuroscience, CLA
Councilor, Philadelphia Chapter of the Society for Neuroscience
Ad-Hoc Reviewer, NIH Pathophysiological Basis of Mental Disorders and Addictions Study Section – 2019
Member, Psychology Department Faculty Awards Committee
Member, Psychology Department Undergraduate Curriculum Committee
Member, Neuroscience Program Curriculum Committee
Member, Psychology Department Faculty Search Committee
Member, Internal Advisory Committee, NIDA T32 Institutional Training Grant

Parkson Chong

Member, Editorial Board, *International Journal of Molecular Sciences*, 2017-2019
Member, Editorial Board, *AIMS Biophysics*
Guest Editor, "*Biochemistry and Biophysics of Archaea Membranes*", *International Journal of Molecular Sciences,* 2019
Member, NSF panel, 2003-2018
Reviewer, the Marion Milligan Mason Award for Women in the Chemical Sciences, AAAS, 2015-2018
Leader, Molecular and Cellular Biosciences Cluster, Biomedical Science Graduate Program, Lewis Katz School of Medicine, Temple University, 2012-present

Alan Cowan

Temple University LKSOM Delegate, US Pharmacopeia Convention

Toby Eisenstein

Member, Editorial Board, *Journal of Neuroimmune Pharmacology*, 2011-present
Member, Eastern Pennsylvania Branch of the American Society for Microbiology
Chair, Academic Affairs Committee
Member, Executive Committee
Member, Board of Directors of the College on Problems of Drug Dependence, June 2013 – June 2017
Councilor, Society on Neuroimmune Pharmacology 2017-
CSAR Seminar Coordinator, 2016-2020
Chair, Appointments, Promotion and Tenure Committee, Dept of Microbiology & Immunology.
Chair, CSAR Faculty Search Committee 2017-2018
Member, Medical Faculty Senate Nominating Committee
Member, Medical Faculty Senate Steering Committee
Member, Strategic Finance Planning Committee (Medical School) 2018

Lynn Kirby

Ad-hoc reviewer, NIH Special Emphasis Panel/SRG: Emerging Technologies in Neuroscience [ZRG1ETTN-D (02)], 2017
Ad-hoc reviewer, Netherlands Organization for Scientific Research, external ad hoc proposal review for Open Programme for Earth and Life Sciences, 2018
Ad-hoc reviewer, Netherlands Organization for Scientific Research, external ad hoc proposal review for TOP grant programme, 2018
Ad-hoc reviewer, NIH Special Emphasis Panel/2019/05 ZRG1 MDCN-R (86) A - Neuroscience AREA Grant Applications, 2019
Member, Media Relations Committee, College on Problems of Drug Dependence, 2019 – 2022
External Examiner, Swarthmore College Honors Program, Dept.Psychology, 2002-Present
Co-director, Neuroscience Cluster, Biomedical Graduate Program, LKSOM, 2006 - Present
Vice Chair, Institutional Animal Care and Use Committee, 2019 - Present (member since 2014)
Member, Faculty Appointment/Promotion Review Committee, LKSOM, 2018-2021
Member, Committee on the Status of Women Faculty in Medicine, 2013 - Present
Member, LCME Educational Programs Subcommittee, LKSOM, 2015 - 2017
Member, Small Animal User Committee, LKSOM, 2015 - Present
Member, Graduate Program Committee, LKSOM, 2015 - Present
Member, Substance Abuse Curriculum Committee, LKSOM, 2017 - Present
Member, Faculty Appointments and Promotions Committee, LKSOM, 2018 - 2021
Member, Search Committee for the Director, Shriners Hospitals for Children Pediatric Research Center at Temple University, 2019 - Present
Member, Faculty Tenure/Promotion Committee, Dept Anatomy and Cell Biology, LKSOM, 2014 - Present
Member, Faculty Search Committee, Dept Anatomy and Cell Biology, LKSOM, 2017- 2018
Member, Faculty Search Committee, Center for Substance Abuse Research, LKSOM, 2017- 2018
Member, Faculty Appointment/Promotion Review Committee, Center for Substance Abuse Research, LKSOM, 2017 - Present
Chair, Animal Use Committee, Center for Substance Abuse Research, LKSOM, 2014 - Present

Lee-Yuan Liu-Chen

Treasurer, International Narcotics Research Conference, 2018-2022
Speaker, Symposium on Biased Signaling, International Narcotics Research Conference, 2019 New York, NY
Member, Program Committee, The Kappa Therapeutics 2019 Conference, Seattle, WA
Chair, Oral Session on "Dynorphins in Disease", The Kappa Therapeutics 2019 Conference, Seattle, WA
Member, Organizing Committee, International Narcotics Research Conference, 2018, San Diego, CA
Chair, Symposium on "Kappa, Novel Uses" in International Narcotics Research Conference, 2018, San Diego, CA
Member, Assessment Committee, charged with evaluation of Graduate Institute of Clinical Pharmacy, School of Pharmacy, National Taiwan University, Taipei, Taiwan, 2018
Guest lecturer, gave a 2-hour lecture on "Drug Abuse" in the course *Neuropsychopharmacology*, School of Pharmacy, National Taiwan University, Taipei, Taiwan, 2018
Chair, Organizing Committee, The Kappa Therapeutics 2017 meeting, Philadelphia, PA
Member, Program Committee of the Kappa Therapeutics 2017 meeting, Philadelphia, PA

External Examiner, Bradley Nash PhD thesis defense, Department of Physiology and Pharmacology, Drexel University School of Medicine, 2017
Ad-Hoc Reviewer, NIH MDCN N04 Study section, 2017
Ad-Hoc Reviewer, NIH NIDA CEBRA Study Section, 2017
Ad-Hoc Reviewer, NIH SYN Special Emphasis Panel, 2018
Ad-Hoc Reviewer, Discovery Grants Program, National Science and Engineering Research Council of Canada, 2018
Ad-Hoc Reviewer, The Research Grants Council, Hong Kong, 2018
Ad-Hoc Reviewer, NIH MNPS Study Section, June 2019
Member, MFS Research and Scholarship Committee
Member, MFS Finance Committee
Chair, Appointment, Promotion and Tenure Committee, Department of Pharmacology, LKSOM
Co-Chair, CSAR Equipment Committee
Chair, CSAR Appointment, Tenure and Promotion Committee
Member, CSAR Faculty Search Committee 2017-2018
Member, Internal Advisory Committee, NIDA T32 Institutional Training Grant

Mary F. Morrison

Trustee, The College of Physicians of Philadelphia, 2018-
Member, NIMH Translational Neuropsychopharmacology Task Force, 2017-
Member, Sex and Gender Women's Health Collaborative Scholarship Committee, 2014-18
DSMB Member, "SSRI Effects on Depression and Immunity in HIV/AIDS", D Evans PI, 2017-

John Muschamp

Member, CSAR Laboratory Animal Facility Space and Resource Allocation Committee, 2014-present
Member, CSAR Laboratory Safety Committee, 2014- present
Ad Hoc Reviewer, NIH, *Molecular Neuropharmacology and Signaling* Study SRG, 2017

Vinay Parikh

Chair, Symposium – "Nicotinic cholinergic signaling in neurological and psychiatric disorders: Insights from mouse models." 27th Annual IBNS Meeting, Boca Raton, FL, 2018
Chair, Scientific Panel – "Emerging insights into the cellular and cognitive substrates of nicotine addiction." 50th Annual Winter Conference on Brain Research, Big Sky, MT, 2017
Associate Editor, *Frontiers in Integrative Neuroscience*, 2018 – present
Member, Editorial Board, *European Journal of Neuroscience*, 2010 – present
Member, Temple University IACUC Committee, 2017 – present
Director, Temple University – CLA Neuroscience Program, 2016 – 2019
Member, Education and Training Committee, ACNP, 2018 – present
Ad Hoc Reviewer, NIH Special Emphasis Panel (ZRG1 IFCN-T-02-M), 2015-2016
Ad Hoc Reviewer, CUNY Research Foundation Program, 2019
Ad Hoc Reviewer, Biotechnology and Biological Sciences Research Council (UK), 2016-present
Member, Operations Committee, Department of Psychology, 2017-present
Member, Graduate Committee, Department of Psychology, 2016-present
Chair, Neuroscience Planning Committee, Department of Psychology, 2016-2017
Member, Faculty Search Committee, Department of Psychology

Yuri Persidsky

Member, Editorial Board, *Journal of Neuroimmune Pharmacology,* 2006-present
Journal of NeuroVirology, 2006-present
Barriers of the CNS, 2010-present
Tissue Barriers, 2012-present
American Journal of Pathology, 2013-present
Ad hoc reviewer, Parkinson's Research Program, Idea Award/Focused
Idea Award Funding Opportunity Number: W81XWH-16-PRP-FIA, US
Ad hoc reviewer, NIH Director's Early Independence Award Rev., ZRG1 RPHB-W (53) R, 2017
Member, Review panel NZ4, National Science Centre, Poland
Ad hoc reviewer, ZAA1 DD (14/15) FRA-AA-17-014 Collaborative Research in HIV/ADIS, Alcohol and related comorbidities
Ad hoc reviewer, Agence Nationale de la Recherche, ANR (Paris, France)
Ad hoc reviewer, ZDA1 SXM-M (01) S (T32) Ruth L. Kirschstein National Research Service Award (NRSA) Institutional Research Training Grants, 2018
Chair, ZMH1 ERB-X (03) S National NeuroAIDS Tissue Consortium, 2018
Ad hoc reviewer, ZRG1 Clinical Neuroimmunology and Brain Tumors Study Section W (06) S, 2019
Ad hoc reviewer, AA1 Study Section, NIAAA, NIH
Ad hoc reviewer, AA4 Study Section, NIAAA, NIH
Ad hoc reviewer, BDCN-W (03) M Study Section, NIH
Ad hoc reviewer, ZRG1 Clinical Neuroimmunology and Brain Tumors Study Section, 2019
Ad hoc reviewer, ZAA1 DD (61) Comprehensive Alcohol- HIV/IDS Research Center, RFA AA 19-003, 2019
Member, International Scientific Committee for 13th International Conference on Cerebral Vascular Biology, June 2019, Miami (USA).
Member, Meritorious Awards Committee, American Society of Investigative Pathology
Chair, LKSOM Research Strategic Planning Committee

Servio H. Ramirez

Director, Histopathology Research Core, Department of Pathology & Laboratory Medicine (LKSOM), 2011–Present
Member, LKSOM MD/PhD Program Admissions Committee, 2008-Present
Member, LKSOM Liaison Committee on Medical Education, 2015- 2017
Member, Institutional Animal Care & Use Committee (IACUC), 2016-Present
Member, LKSOM Medical Faculty Senate: Diversity committee, 2018-Present
Member, Invention and Patent Committee, Temple University, 2015- Present
Member, LKSOM Appointment & Promotion Committee, Dept. of Pathology & Laboratory Medicine, 2016-Present
Member, LKSOM Faculty Development Committee, Dept. of Pathology & Laboratory Medicine, 2018–Present
Grant Reviewer, The Portuguese Foundation for Science & Technology, Israel Science Foundation (ISF), United Kingdom Medical Research Council (MRC), The French national agency for the promotion of higher education
Standing Member Reviewer, NIH/CSR Brain Injury & Neurovascular Pathologies (BINP) study section, 2015-2019

Ad-hoc Reviewer, NIH/CSR NeuroAids & End-Organ Diseases (NAED) Study Section, 2015-2017
Standing Member Reviewer, American Heart Association: Vascular Endothelial Biology and Function - Basic Science IV study section, 2013-2016
Standing Member Reviewer, Combat Casualty Care Research Program (CCCRP) for the CDMRP's Defense Medical Research and Development Program (DMRDP) NeuroTrauma session, 2017-Present
Society on Neuroimmune Pharmacology (SNIP):
Member, Early Career Investigator Travel Award (ECITA) committee, 2013-Present
Member, Diversity and Inclusion SNIP Committee (DISC), 2013- Present
Member External Advisor Committee for the University of Rochester's Training in HIV replication and pathogenesis" 5T32AI049815, NIH/NIAID, 2018- Present
Academic Editor, PLoS ONE, 2010-Present
Member, Editorial Board *Clinical Research in HIV/AIDS*, 2013-Present
Member, Editorial Board *Frontiers In Molecular Neuroscience*, 2019-Present

Scott Rawls

Member, LKSOM MD/PhD Program Advisory Committee, 2012-2018
Member, LKSOM Dean's Advisory Committee, 2017-18
Member, CSAR Faculty Search Committee, 2017
Member, MFS Steering Committee, 2019
Member, LKSOM Academic Standards and Promotion Committee, 2018-present
Member, LKSOM Temple Medical Honor Boards, 2018-present
Member, MFS Faculty Development Committee, 2019
Member, MFS Research Strategic Planning Committee, 2018-2019
Ad Hoc Reviewer, ZRG1 BCMB-U (50) National Institute on Drug Abuse Special Emphasis Panel (PAR16-383/384 review panel for chemical probes for drug addiction), 2017
Ad Hoc Reviewer, ZRG1 MDCN-G (04) National Institute on Drug Abuse Special Emphasis Panel (PAR on Synthetic Psychoactive Drug Abuse) Meeting (Co-Chair), 2018
Ad Hoc Reviewer, ZRG1 MDCN-R (56) M National Institute on Drug Abuse Special Emphasis Panel (PAR on Synthetic Psychoactive Drug Abuse) Meeting, 2019
Member, Internal Advisory Committee, NIDA T32 Institutional Training Grant

Zachary Reichenbach

Fellow, Gastroenterology and Hepatology, Temple University Hospital, 2018-present
Resident, Internal Medicine, Temple University Hospital, 2017-2018
Member, Pre-Professional Health Studies Evaluation Committee, Temple University, 2017-present
Interviewer, Admissions Committee, Lewis Katz School of Medicine, 2017-present
Editor, Academic Stroke Journal, 2019-present
Editor, Asia Pacific Journal of Clinical Trials, Nervous System Diseases, 2017-present

Thomas Rogers

Section Editor (Cell Signaling and Immunity), *Journal of Neuroimmune Pharmacology*, 2006- present
Member, Editorial Board, *Journal of Leukocyte Biology*, 1999-present
Member, Communications Committee, Society for Leukocyte Biology, 2017-present
Study Section, NIH Special Emphasis Panel, ZRG1 SXM-M (09), 2017
Study Section, NIH Special Emphasis Panel, ZRG1 AARR-N (91) S, 2017

Study Section, NIH Special Emphasis Panel, ZRG1 AARR-N (91) P, 2017
Study Section, NIH Special Emphasis Panel, ZRG1 AARR-K (58) 2017
Study Section, NIH Special Emphasis Panel, ZRG1AARR-K (92), 2017
Study Section, Ad hoc reviewer, NIH NAED study section, 2018
Study Section, NIH Special Emphasis Panel, ZRG1 AARR-Q (51), 2018
Study Section, Ad hoc reviewer, NIH ACE study section, 2019
Temple University Institutional Biosafety Committee, member 2012-present
Chair, Temple University Institutional Biosafety Committee, 2018-present
Director, Temple University Flow Cytometry Facility, 2006-present
Chair, Faculty Search Committee, Department of Thoracic Medicine and Surgery, 2017-present
Member, Faculty Search Committee for Chair of Fels Institute for Cancer Research and Molecular Biology, 2019-present

Slava Rom

Member, BMSC Admissions Committee, 2019-present
Member, University Senate Research Programs and Policies Committee (RPPC), 2019-present
Member, LKSOM representative to the University Faculty Senate, 2016-present
Ad-hoc reviewer, NIH Special Emphasis Panel/Scientific Review Group ZRG1 MDCN-M (91), 2018-2019
Manager, Flow Core in Department of Pathology and Laboratory Medicine, 2014-present

Stephanie Sillivan

Member, BSMC Curriculum Committee
Member, PA Student Performance Committee
Member, CSAR Equipment Committee

Ronald Tuma

Member, Editorial Board, *Microvascular Research*, 1990-present
Member, Editorial Board, *Autoimmune Diseases*, 2010-present
Member, BMSC Admissions Committee
Member, PA Program Curriculum Committee

Ellen Unterwald

Councilor, Philadelphia Chapter of the Society for Neuroscience
Councilor, Mid-Atlantic Pharmacology Society
Ad Hoc Reviewer, NIDA-K Pathway to Independence Awards, Career Development Awards, and Institutional Training Grants, 2017-2019
Ad Hoc Reviewer, NIH Special Emphasis Panel, BCMB-W, 2017
Ad Hoc Reviewer, NIH Neurobiology of Motivated Behaviors, 2019
External Advisor, NIDA-funded training program, Weill College of Medicine, Cornell University, New York
External Advisor, NIDA-funded training program, Oregon Health Sciences University, Portland
External Advisor, NIDA-funded training program, University of Pennsylvania Pearlman School of Medicine
Internal Advisor, NIGM training program application, Fels Institute, LKSOM

Co-Chair, Temple University Taskforce on Opioid and Other Substance Abuse, 2018-2019
Chair, LKSOM Small Animal User Committee
Medical Education Subcommittee: Safe opioid prescribing and treatment of substance use disorders
Member, LKSOM Dean's Advisory Committee, 2016-2019
Member, TUH/LKSOM Opioid Abuse Taskforce, 2017-2019
Member, LKSOM Conflict of Interest Committee, 2016-present
Member, LKSOM Strategic Planning Finance Committee, 2018-2019

Sara Ward

Councilor, Philadelphia Chapter of the Society for Neuroscience, 2008- present
Member, International Cannabinoid Research Committee Program Committee, 2018
Member, LKSOM Student Learning Environment and Appeals Committee, 2018-present
Member, CSAR Laboratory Animal Facility Space and Resource Allocation Committee, 2014-present
Member, Post Baccalaureate Advisory Committee, 2016-present
Member, Post baccalaureate Curriculum Committee, 2016-present
Member, LKSOM Medical Faculty Senate Steering Committee, 2019
Ad hoc reviewer, Department of Defense Gulf War Illness Research Program Awards, 2019
Ad hoc reviewer, NIH Somatosensory and Pain Study Section, 2019
Ad hoc reviewer, Canadian Institutes of Health Research Team Grant: Cannabis Research in Priority Areas Initiative, 2019

Ellen Walker

Chair, Department of Pharmaceutical Sciences, School of Pharmacy, 2017-present
Advisory Board, World Health Organization, Expert Committee on Drug Dependence, 2010-present
External Advisory Board Member, NIDA T32 Institutional Training Grant to Department of Pharmacology at University of Texas Health Science Center, 2015-2019
Treasurer, Philadelphia Chapter of the Society for Neuroscience, 2016-present
Co-Chair, symposium on "Atypical Opioids," International Narcotics Research Conference, 2019, New York, NY
Chair, Temple University Institutional Animal Care and Use Committee, 2018-present
Member, Provost's Academic Program Advisory Committee, 2016-2018
Member, University Tenure and Promotion Committee, 2018-2019
Member, Professional Curriculum Committee, School of Pharmacy, 2017-present
Member, Research Day and Awards Committee, School of Pharmacy, 2017-present

Mathieu Wimmer

Vice President, Philadelphia Chapter of the Society for Neuroscience, 2018-2019
President, Philadelphia Chapter of the Society for Neuroscience, 2019-present
Member, Diversity Committee, Temple University Department of Psychology (CLA)
Member, NSCI Committee, Temple University Department of Psychology (CLA)
Ad-hoc Reviewer for Avenir mail in study section, NIDA
Member, ACE Task Force Temple University

Grants Related to Drugs of Abuse Awarded to Researchers in CSAR

PRINCIPAL INVESTIGATOR/MPI (Co-Investigator)	GRANT TITLE	SOURCE GRANT NUMBER FUNDING PERIOD	TOTAL AWARD AMOUNTS
Abood	Molecular Characterization of GPR35 and GPR55, Putative Cannabinoid Receptors	NIH/NIDA R01 DA023204 06/15/2012-05/31/2017	Direct: $ 691,486 Indirect: $ 187,302 Total: $ 878,788
Abood/Benamar MPI (Kirby Co-I)	Functional Role for GPR55 in the Periaqueductal Gray	NIH/NIDA R01 DA035926 04/01/2014-03/31/2019	Direct: $ 994,200 Indirect: $ 557,500 Total: $ 1,551,700
Abood (PI: A. Makriyannis, Northeastern Univ)	Endocannabinoid Active Sites as Therapeutic Targets (subcontract)	NIH/NIDA P01 DA009158 09/14/2014-06/30/2019	Direct: $ 28,272 Indirect: $ 15,832 Total: $ 44,104
Abood (PI: P.H. Reggio, UNC Greensboro)	Molecular Determinants of Cannabinoid Activity (subcontract)	NIH/NIDA R01DA003934 07/01/2015-06/30/2020	Direct: $ 35,423 Indirect: $ 19,736 Total: $ 55,159
Abood/P.H.Reggio, UNC Greensboro, MPI	Molecular Determinants for GPR55 Activity	NIH/NIDA R01 DA045698 05/15/2018-03/31/2023	Direct: $ 1,260,560 Indirect: $ 597,790 Total: $ 1,858,350
Adler (Co-I: Eisenstein, Rawls, Cowan)	Enhanced Chronic Pain Management Utilizing Chemokine Receptor Antagonists	Department of Defense W81XWH-15-1-0252 07/15/2015-07/14/2019	Direct: $ 1,886,018 Indirect: $ 999,586 Total: $ 2,885,604

Grants Related to Drugs of Abuse Awarded to Researchers in CSAR

PRINCIPAL INVESTIGATOR/MPI (Co-Investigator)	GRANT TITLE	SOURCE GRANT NUMBER FUNDING PERIOD	TOTAL AWARD AMOUNTS
Bangasser	Chronic Stress Regulation of Attention Circuits	PA Dept Health PA CURE 01/01/2017-12/31/2019	Direct: $ 100,000 Indirect: $ 0 Total: $ 100,000
Bangasser	Chronic Stress-induced Transcriptional Changes in Cholinergic Neurons	iGEM Award for Genomics Temple University 03/01/2017-02/28/2018	Direct: $ 10,000 Indirect: $ 0 Total: $ 10,000
Bangasser	CAREER: Interactions between Stress and Attention Circuits: Investigating Corticotropin-Releasing Factor Modulation of the Basal Forebrain	NSF/IOS NSF CAREER-1552416 03/01/2016-02/28/2021	Direct: $ 566,317 Indirect: $ 309,032 Total: $ 875,350
Barrett (PI: L. Kuo, Mebias Discovery; Co-I: Rawls)	Biased Mu-Opioid Receptor Analgesics to Prevent Overdose and Opioid Use Disorders (subcontract)	NIH/NIDA UG3 DA047700 09/15/2018-08/31/2020	Direct: $ 557,943 Indirect: $ 312,323 Total: $ 870,266
Briand	AMPA Receptor Trafficking and Cocaine Reinstatement	NIH/NIDA R00 DA033372 02/01/2015-01/31/2018	Direct: $ 471,744 Indirect: $ 264,174 Total: $ 735,918
Briand	Examining Mechanisms Underlying Drug-Associated Memory Erasure by Zeta-Inhibitory Peptide	NIH/NIDA R01 DA047265 04/15/2019-01/31/2024	Direct: $ 1,433,002 Indirect: $ 893,207 Total: $ 2,436,209
Eisenstein	Novel Peptide Chemokine Receptor Antagonists for Combating the Opiate Epidemic	Creative Bio-Peptides, Inc 12/01/2017-05/31/2018	Direct: $ 28,636 Indirect: $ 2,864 Total: $ 31,500
Ho	Opioid, HIV/HCV and Host Cell Innate Immunity	NIH/NIDA R01 DA022177 07/01/2013-02/28/2018	Direct: $ 897,400 Indirect: $ 336,875 Total: $ 1,234,275

Grants Related to Drugs of Abuse Awarded to Researchers in CSAR

PRINCIPAL INVESTIGATOR/MPI (Co-Investigator)	GRANT TITLE	SOURCE GRANT NUMBER FUNDING PERIOD	TOTAL AWARD AMOUNTS
Ho	Methamphetamine, Innate Immunity and HIV	NIH/NIDA R01 DA041302 07/1/2016-05/31/2021	Direct: $1,125,000 Indirect: $ 630,000 Total: $1,755,000
Ho	Opioids, Extracellular Vesicles, and BBB Innate Immunity	NIH/NIDA R21 DA042373 06/1/2017-05/31/2020	Direct: $ 275,000 Indirect: $ 160,825 Total: $ 423,825
Ho	Role of miRNAs in Methamphetamine/HIV-Mediated Immune Activation	NIH/NIDA R01 DA045568 04/1/2018-02/28/2023	Direct: $1,250,000 Indirect: $ 731,250 Total: $1,981,250
Kirby	Regulation of 5-HT Circuits by CRF and GABA in Opioid Addiction and Stress-Induced Relapse	NIH/NIDA R01 DA045771 01/15/2019-11/30/2023	Direct: $1,125,000 Indirect: $ 611,350 Total: $1,736,350
Liu-Chen	Pharmacology of Kappa Opioid Receptor	NIH/NIDA R01 DA041359 09/15/2017-06/30/2022	Direct: $1,804,356 Indirect: $ 947,925 Total: $2,752,281
Liu-Chen	Kappa Opioid Receptor in Claustrum	NIH/NIDA R21 DA045274 09/30/2018-08/31/2020	Direct: $ 275,000 Indirect: $ 160,875 Total: $ 435,875
Liu-Chen (PI: D.Y.W. Lee, McLean Hosp/Harvard Univ; Co-I: Ward)	Mechanism of Action of L-THP as an Alternative Therapy for Cocaine Addiction (subcontract)	NIH/NCCIH R01 AT006899 09/01/2012-06/30/2017	Direct: $ 750,000 Indirect: $ 375,000 Total: $1,125,000
Muschamp	Role of Orexin (Hypocretin) in Impulsive Behavior	NIH/NIDA R00 DA031767 07/01/2012-04/30/2017	Direct: $ 790,095 Indirect: $ 442,450 Total: $1,232,545

Grants Related to Drugs of Abuse Awarded to Researchers in CSAR

PRINCIPAL INVESTIGATOR/MPI (Co-Investigator)	GRANT TITLE	SOURCE GRANT NUMBER FUNDING PERIOD	TOTAL AWARD AMOUNTS	
Muschamp	Orexin-dynorphin Signaling in Models of Affect	Landenberger Foundation 07/15/2015-07/14/2017	Direct: Indirect: Total:	$ 200,000 $ 0 $ 200,000
Persidsky	Novel CB2 Agonists Shield Brain From HIV Infection and Alcohol Exposure	NIH/NIAAA U01 AA023552 02/05/2016-01/31/2021	Direct: Indirect: Total:	$ 1,125,000 $ 630,000 $ 1,755,000
Persidsky	BBB Protection In HIV Infection: Barrier-Shielding Effects of PARP Inhibition	NIH/NIMH R01 MH065151 07/01/2012-06/30/2017	Direct: Indirect: Total:	$ 1,555,598 $ 518,533 $ 2,074,131
Persidsky	CNS Injury Caused by HIV-1 and Alcohol: Protective Effects of CB2 Activation	NIH/NIAAA R37 AA015913 05/01/2015-04/30/2020	Direct: Indirect: Total:	$ 1,187,080 $ 664,765 $ 1,851,845
Persidsky (Co-I: Unterwald)	BBB Injury In HIV Infection Complicated by Diabetes: Mechanisms and Protective Strategies Preventing Cognitive Impairment	NIH/NIMH R01 MH115786 07/1/2018-04/30/2023	Direct: Indirect: Total:	$ 1,645,175 $ 962,426 $ 2,607,601
Ramirez (Tuma & Kirby)	Mechanisms and Treatment Strategies to Counter Addiction Susceptibility Post-TBI	PA Dept Health SAP410077079 01/01/2017-12/31/2020	Direct: Indirect: Total:	$ 3,465,150 $ 534,850 $ 4,000,000
Ramirez	Novel Serological Biomarkers for BBB Dysfunction during HIV-1 Infection	NIH/NINDS R01 NS086570 09/30/2013-08/31/2018	Direct Indirect: Total:	$ 1,000,000 $ 560,000 $ 1,560,000
Ramirez/Potula MPI (Co-I: Rawls)	Brain Endothelial EVS Role in the Neuropathology of Drugs of Abuse and HIV	NIH/NIDA R01 DA046833 09/30/2018-06/30/202	Direct: Indirect: Total:	$ 1,684,935 $ 985,685 $ 2,670,620

Grants Related to Drugs of Abuse Awarded to Researchers in CSAR

PRINCIPAL INVESTIGATOR/MPI (Co-Investigator)	GRANT TITLE	SOURCE GRANT NUMBER FUNDING PERIOD	TOTAL AWARD AMOUNTS	
Rawls (Co-I:Ward)	Psychoactive Bath Salts and the Glutamate System	NIH/NIDA R01 DA039139 09/15/2015-07/31/2020	Direct: Indirect: Total:	$ 1,227,914 $ 608,664 $ 1,836,578
Rawls (Co-I:Ward)	Planarians and the Pharmacology of Addiction: an In Vivo Model for K-12 Education	NIH/NIDA/OD R25 DA033270 07/15/2014-06/30/2018	Direct: Indirect: Total:	$ 957,615 $ 54,659 $ 1,012,274
Rawls	Therapeutic Secrets of Kratom in Preclinical Neuropathic Pain and Abuse Liability Models and Characterization of Underlying Opioid and Adrenergic Mechanisms	NIH/NICCH R21 AT010404 04/8/2019-03/31/2021	Direct: Indirect: Total:	$ 275,000 $ 160,875 $ 435,875
Rawls/Unterwald MPI	Chemokine CXCL12/CXCR4 System and Synthetic Cathinones	NIH/NIDA R01 DA045499 07/1/2018-04/30/2023	Direct: Indirect: Total:	$ 1,228,180 $ 680,065 $ 1,908,245
Rawls	Drug Addiction Education Program	PA Dept of Health PA CURE/Temple 07/01/2018-/2/31/2020	Direct: Indirect: Total:	$ 100,000 $ 0 $ 100,000
Rawls (MPI: A. Reitz, Fox Chase Chemical Diversity Center)	Trigriluzole for the Treatment of Cocaine Addiction (subcontract)	NIH/NIDA R41 DA047169 07/1/2018-06/30/2020	Direct: Indirect: Total	$ 113,565 $ 66,435 $ 180,000
Roger/Persidsky MPI	HIV-induced Neuroinflammation Associated with Opioid Abuse and Tobacco Smoke	NIH/NIDA R01 DA040619 08/16/2016-05/31/2021	Direct: Indirect: Total:	$ 2,030,159 $ 1,246,087 $ 3,276,246
Roger/Persidsky MPI	Inflammation Associated with HIV Infection: Role of Receptor Cross-talk	NIH/NIDA R01 DA049745 09/30/2019-06/30/2024	Direct: Indirect: Total:	$ 2,110,500 $ 1,189,890 $ 3,300,390

Grants Related to Drugs of Abuse Awarded to Researchers in CSAR

PRINCIPAL INVESTIGATOR/MPI (Co-Investigator)	GRANT TITLE	SOURCE GRANT NUMBER FUNDING PERIOD	TOTAL AWARD AMOUNTS
Rogers	Interactions between Opioid and Chemokine Receptors Relative to HIV	NIH/NIDA R01 DA014230 03/15/2012-05/31/2017	Direct: $ 1,125,000 Indirect: $ 589,095 Total: $ 1,714,095
Rom	Protective Role of LET-7 MicroRNAs in Brain Endothelial Dysfunction During Ischemia/ Reperfusion Injury	NIH/NINDS R01 NS101135 2/1/2017-11/30/2022	Direct: $ 1,028,125 Indirect: $ 594,019 Total: $ 1,622,144
Sawaya	Involvement of HIV-1 VPR in Neuronal Degeneration	NIH/NINDS R01 NS076402 09/30/2011-07/31/2017	Direct: $ 1,237,500 Indirect: $ 655,875 Total: $ 1,893,375
Sawaya	PGC-1 Alpha and Reelin: New Players in HAND Progression	NIH/NIA R01 AG054411 09/30/2017-05/31/2022	Direct: $ 1,250,000 Indirect: $ 731,250 Total: $ 1,981,250
Sillivan	MicroRNA-Mediated Mechanisms of Heroin Drug Seeking	NIH/NIDA R00 DA041469 09/01/2018-07/31/2021	Direct: $ 464,997 Indirect: $ 272,024 Total: $ 737,021
Tuma	Development of an Optimized Cannabinoid-Based Pharmacotherapy to Attenuate Secondary Injury	PA Dept of Health PA CURE /Temple 07/1/2016-06/30/2019	Direct: $ 100,000 Indirect: $ 0 Total: $ 100,000
Tuma (Co-I: Ward)	Statins and CBD: Interactive Effects	Indication Bioscience 01/01/2019-12/31/2019	Direct: $ 80,500 ndirect: $ 47,082 Total: $ 127,692
Unterwald (Co-I:Liu-Chen)	Training Program: Drugs of Abuse and Related Neuropeptides	NIH/NIDA T32 DA007237 07/01/2015-06/31/2020	Direct: $ 2,307,200 Indirect: $ 161,535 Total: $ 2,468,735

Grants Related to Drugs of Abuse Awarded to Researchers in CSAR

PRINCIPAL INVESTIGATOR/MPI (Co-Investigator)	GRANT TITLE	SOURCE GRANT NUMBER FUNDING PERIOD	TOTAL AWARD AMOUNTS	
Unterwald	Regulation of Delta Opioid Receptor Function by Cocaine	NIH/NIDA R01 DA018326 04/01/2012-03/31/2017	Direct: Indirect: Total:	$ 1,088,000 $ 445,200 $ 1,533,200
Unterwald (Eisenstein, Adler, Rawls, Liu-Chen, Rogers)	Center on Intersystem Regulation by Drugs of Abuse	NIH/NIDA P30 DA013429 05/01/2015-04/30/2020	Direct: Indirect: Total:	$ 4,513,405 $ 2,529,694 $ 7,039,099
Unterwald	Individual Differences in Susceptibility to PTSD and Co-morbid Substance Abuse)	NIH/NIDA R03 DA044483 09/01/2017-08/31/2019	Direct: Indirect: Total:	$ 100,000 $ 58,500 $ 158,500
Unterwald	GSK3Beta Signaling in Cocaine Reward and Memory	NIH/NIDA R01 DA043988 09/01/2017-06/30/2022	Direct: Indirect: Total:	$ 1,250,000 $ 731,250 $ 1,981,250
Unterwald	GSK3Beta Signaling in Cocaine Reward and Memory	NIH/NIDA R01 DA043988-S1 09/01/2017-06/30/2022	Direct: Indirect: Total:	$ 104,233 $ 60,976 $ 165,209
Unterwald (Co-I; Barr, PI)	Cocaine Regulation of Hilar Mossy Cell Activity	NIH/NIDA R03 DA040747 08/15/2016-08/31/20187	Direct: Indirect: Total:	$ 100,000 $ 56,000 $ 156,000
Walker	Evaluation of Synthetic Opioid Substances	DEA contract DJD-17-HQ-P-0646 08/30/2017-09/30/2018	Direct: Indirect: Total:	$ 67,405 $ 39,432 $ 106,837
Walker	Evaluation of Synthetic Opioid Substances	DEA contract DJD-18-HQ-P-0646 10/01/2018-09/30/2019	Direct: Indirect: Total:	$ 67,405 $ 39,432 $ 106,837

Grants Related to Drugs of Abuse Awarded to Researchers in CSAR

PRINCIPAL INVESTIGATOR/MPI (Co-Investigator)	GRANT TITLE	SOURCE GRANT NUMBER FUNDING PERIOD	TOTAL AWARD AMOUNTS
Ward	Development of KLS-13019 for Chemotherapy-Induced Peripheral Neuropathy and Drug Dependence (subcontract)	NIH/NIDA R41 DA044898 01/01/2018-12/31/2019	Direct: $ 110,852 Indirect: $ 64,848 Total: $ 175,700
Ward	Analgesic Efficacy of Single and Combined Minor Cannabinoids and Terpenes	NIH/NCCIH R01 AT010778 09/15/2019-08/31/2024	Direct: $ 1,250,000 Indirect: $ 731,250 Total: $ 1,981,250
Ward	Modulation of Invading and Resident Inflammatory Cell Activation as a Novel Way To Mitigate Spinal Cord Injury-Associated Neuropathic Pain	Department of Defense USAMRAMC-CDMRP W81XWH-14-1-0389 09/01/2014-08/31/2017	Direct: $ 750,000 Indirect: $ 435,000 Total: $ 1,185,000
Ward	A Combined Complementary Cannabinoid Treatment Strategy for Spinal Cord Injury	PA Dept Health PA CURE/Temple 07/01/2016-06/30/2019	Direct: $ 100,000 Indirect: $ 0 Total: $ 100,000
Wimmer	Mechanisms Underlying Deficits Caused by Paternal Cocaine Taking	NIH/NIDA K01 DA039308 05/1/2016-04/30/2021	Direct: $ 824,464 Indirect: $ 65,272 Total: $ 889,736
Wimmer	Unraveling Epigenetic Mechanisms of Opioid Addiction Susceptibility Using Multigenerational Animal Models	NIH/NIDA DP1 DA046537 07/15/2018-5/31/2023	Direct: $ 1,500,000 Indirect: $ 877,500 Total: $ 2,377,500
Wimmer	Unraveling Epigenetic Mechanisms of Opioid Addiction Susceptibility Using Multigenerational Animal Models	NIH/NIDA DP1 DA046537-S1 07/15/2018-05/31/2023	Direct: $ 7,840 Indirect: $ 627 Total: $ 8,467

Grants included in table were actively funded during the period covered by this report (2017-2019), although funding of some of the awards spans the years 2012-2024. Total research funding listed is over $82 million.

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