NIAAA SPECTRUM

Volume 7, Issue 1 | February 2015 | http://www.spectrum.niaaa.nih.gov

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES • National Institutes of Health • National Institute on Alcohol Abuse and Alcoholism

FEATURE

THE INTRAMURAL DIVISION– A CORE COMPONENT OF NIAAA'S RESEARCH PROGRAM

As the lead Federal agency for research on alcohol and health, NIAAA is structured in a way that captures all areas of alcohol science. Through an integrated and multidisciplinary program of basic and applied research, NIAAA investigates everything from the causes, consequences, prevention, and treatment of alcohol use disorder to the potential benefits of moderate drinking. In some cases, NIAAA staff scientists in the Division of Intramural Clinical and Biological Research (DICBR) conduct the research directly; in others, NIAAA's extramural divisions support researchers across the country and around the world.

DICBR is NIAAA's "in-house" research program. With a combination of clinical and basic research (from genetics to molecular biology to neuroimaging), DICBR studies the ways that alcohol produces intoxication, dependence, and damage to vital organs, and the potential tools to prevent and treat those processes.

"At NIH, we have the largest concentration of world-class programs and scientists in the world," says George Kunos, M.D., Ph.D., and Scientific Director of DICBR, speaking of the NIH intramural program broadly. "With nearly 1,000 senior investigators NIH-wide, NIH is an amazing environment in which to conduct basic scientific and clinical research."

The intramural program at NIH also offers unique research opportunities. "We have the ability to do high-risk, high-reward work, which often cannot be done in the extramural community," explains Dr. Kunos. But he is quick to emphasize that the aim of intramural research is "not to compete with extramural research, but to complement it by engaging in innovative approaches."

DICBR's twelve intramural laboratories, some of which are divided into sections, conduct research on many levels, including cellular/molecular studies, animal studies in rodents, human studies of the genetics and epidemiology of alcoholism and co-morbidities, and validation of novel molecular targets for alcohol use disorders.

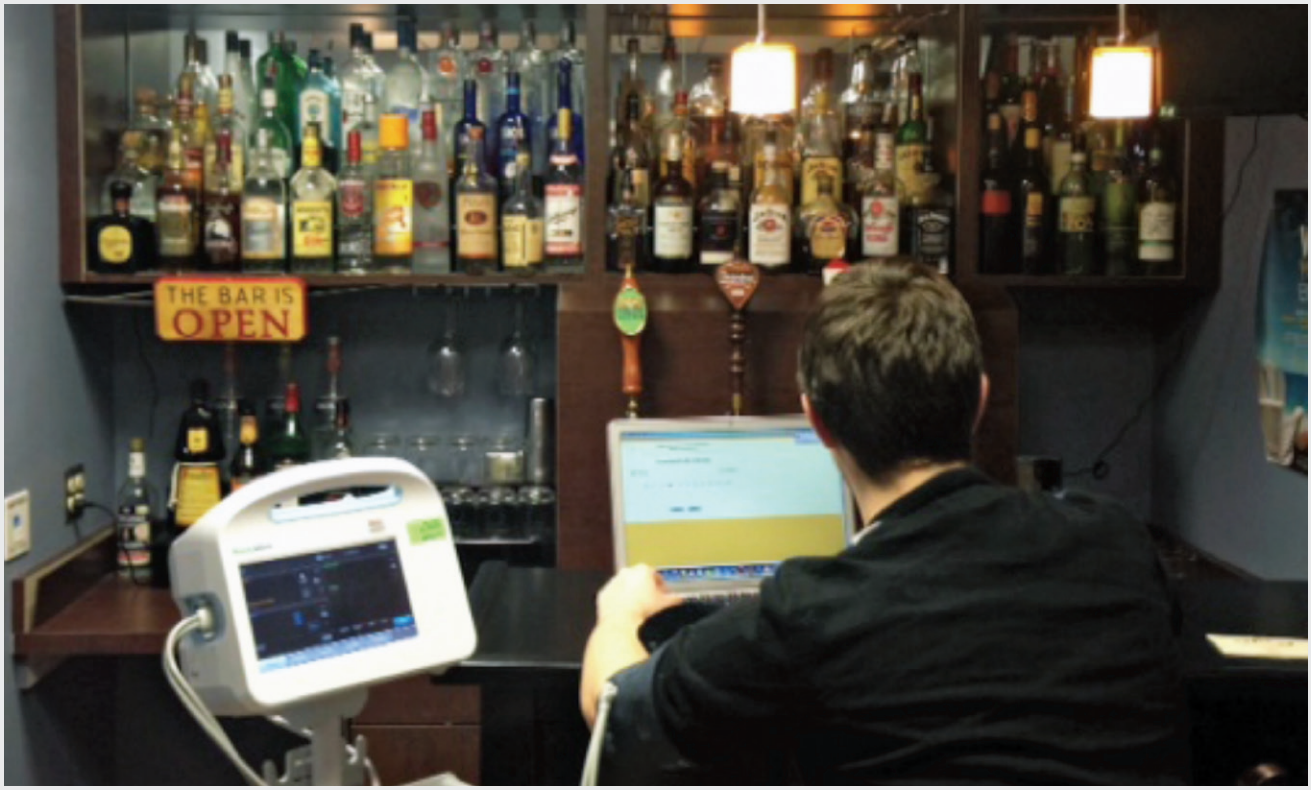
Each lab and section is headed by a principal investigator, tenured or tenure track. Others on the lab teams include staff scientists, staff clinicians, visiting

Continued on page 4

IN THIS ISSUE

A CLOSER LOOK

AN UNUSUAL LAB, BAR NONE



The room looks like your run-of-the-mill neighborhood bar. Soft lighting, an assortment of top shelf liquor three rows deep, and the game on overhead—everything looks and feels familiar. In actuality, researchers have gone to a lot of trouble to mimic an authentic bar experience. And if you were to do a chemical analysis of the bottles overhead, you'd find they contain water with food coloring, tinted to precisely match the color of the bottles' usual contents.

So why the elaborate simulation? This watering hole is actually a laboratory, housed within the NIH Clinical Center, the hospital located on NIH's main campus in Bethesda, Md. The bar lab, used by Lorenzo Leggio, M.D., Ph.D., M.Sc., is an important tool in the hunt for new medications that may help people with alcohol use disorders.

In his current study, Dr. Leggio and his research team are in the initial stages of testing a promising new medication. It works by blocking ghrelin, a hormone produced in the stomach that stimulates appetite, but is also implicated in alcohol craving. This is the first step on the road to determining whether the experimental medication, a compound initially developed by Pfizer to treat diabetes, is safe and effective for individuals with an alcohol use disorder. Results of the safety trial are expected this spring.

In another study conducted in the bar-lab, the same team is testing a medication called baclofen to see if it reduces alcohol craving and use in alcohol dependent individuals with high levels of anxiety.

Subjects sit in the bar lab, soaking up the atmosphere, while measures are taken to evaluate their degree of craving. To heighten the sensory experience, the participant can see and smell his beverage of choice sitting beside him (individualized down to the glass shape and temperature). As pictured above, the subject completes a series of questions about craving levels on a laptop, while a device measures his heart rate and blood pressure. During another session of the experiment, participants choose whether or not to drink alcohol (called "alcohol self-administration").

At present, three medications (naltrexone, acamprosate, and disulfiram) are approved by the U.S. Food and Drug Administration (FDA) for treating individuals with alcohol use disorders. Dr. Leggio and his team are hopeful that their work will increase the range of pharmacologic treatment options for these patients.

FEATURE

NEW GUIDE DESCRIBES ALCOHOL TREATMENT OPTIONS

While an estimated 17 million Americans struggle with problem drinking, only a fraction receive any treatment. No matter how severe the problem may seem, most people with alcohol problems, formally diagnosed as an "alcohol use disorder," can benefit from some type of treatment.

Now, a new resource from the National Institutes of Health (NIH) will help individuals and families understand available treatment options, including those that are effective but underutilized. Developed by the National Institute on Alcohol Abuse and Alcoholism (NIAAA), part of the National Institutes of Health, *Treatment for Alcohol Problems: Finding and Getting Help* covers the latest research-based treatments and what to consider when choosing among them.

"The popular concept of alcohol treatment is often limited to knowledge of inpatient rehab or 12-step programs," said NIAAA Director George Koob, Ph.D.

"In fact there are diverse treatment options of which people may be less aware, many of which can be undertaken with minimal disruption to home and work life. A greater understanding of these options represents an important step toward improving the way we treat alcohol addiction."

The booklet provides detailed descriptions of the two types of professionally-led treatments shown to benefit people with alcohol use disorders—established behavioral treatments which focus on changing drinking behaviors, and medications, which are often coupled with behavioral treatment. It also includes information about mutual-support groups like Alcoholics Anonymous.

Three medications have been approved by the U.S. Food and Drug Administration to help people with alcohol problems stop or reduce their drinking and prevent relapse. These medications—naltrexone, acamprosate, and disulfiram—are non-addictive and can be used alone or in combination with behavioral treatment. All can be prescribed by a primary care physician.

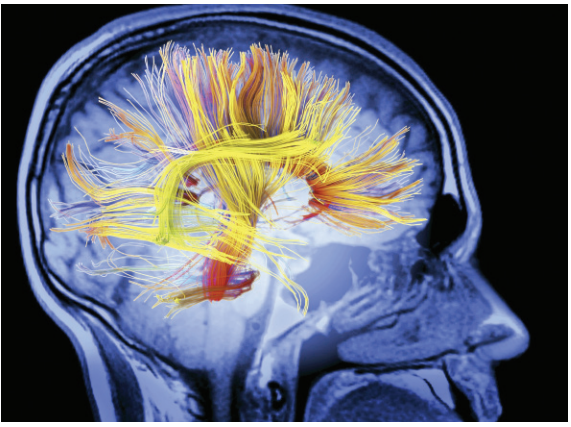
In addition to the discussion of treatment options, the guide offers information on:

- Signs of an alcohol problem
- Questions patients can ask their doctors to help guide their treatment choices
- Advice for friends and family
- New medications in development

Order online at http://pubs.niaaa.nih.gov/publications/treatment/treatment.htm.

NEWS FROM THE FIELD

BRAIN SCANS REVEAL HEAVY DRINKING DAMAGES WHITE MATTER



Researchers led by Catherine Fortier at Harvard Medical School found that chronic alcohol misuse damaged white matter in areas of the brain that are important for self-control and recovery from alcoholism. The findings appeared in the December 2014 issue of *Alcoholism: Clinical & Experimental Research*.

Using high-resolution diffusion magnetic resonance brain scans, the researchers compared a group of 20 healthy light drinkers to a group of 31 individuals with a history of alcoholism. The recovering alcoholics drank heavily for an average of 25 years and had been sober for about five years.

Compared with the light drinkers, the abstinent alcoholics showed pronounced reductions in the structural integrity of frontal and superior white matter tracts. According to the authors, the results suggest altered connectivity in frontostriatal circuits—pathways associated with the amygdala, hippocampus, nucleus accumbens, regions that are involved in the brain's reward system. These networks are essential for controlling impulsive behavior and stopping drinking.

The study also found that longer and heavier alcohol abuse was associated with greater damage. The findings pointed to possible recovery of white matter tissue in drinkers who became abstinent before they turned 50 years of age.

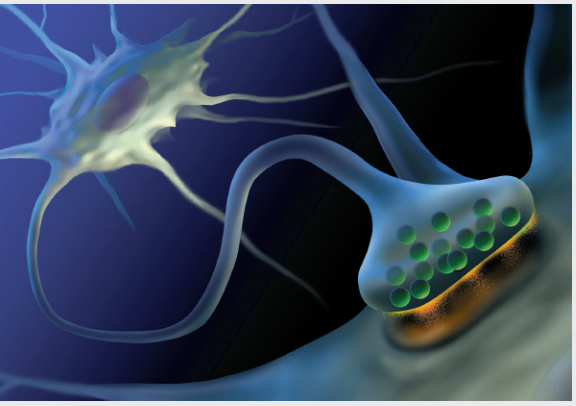
The authors recommend that future investigations should continue to explore white matter changes due to alcohol misuse, including measurements related to the severity of alcoholism and questions about tissue recovery with maintained abstinence.

Source:

Fortier, C.B.; Leritz, E.C.; et al. Widespread effects of alcohol on white matter microstructure. *Alcoholism: Clinical & Experimental Research*. November 18, 2014 [Epub ahead of print]. PMID: 25406797. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25406797

NEWS FROM THE FIELD

STUDY EXPLORES LONG-TERM EFFECTS OF BINGE-LIKE ALCOHOL CONSUMPTION DURING ADOLESCENCE



Binge-like exposure to alcohol during adolescence can lead to deficits in executive function and changes in behavioral control in adulthood, according to a recent study in animals. A team of scientists supported by NIAAA and led by researchers at the Medical University of South Carolina in Charleston, exposed adolescent rats to repeated cycles of alcohol vapor to simulate binge alcohol intoxication. After the animals reached adulthood, the scientists tested them in a series of tasks measuring learning ability and other functions controlled by the brain's prefrontal cortex (PFC). The investigators also conducted brain scans to look for changes in various regions in the brain. The results from these rats were compared with results from a control group of rats that had not been exposed to alcohol in adolescence.

The researchers found that, compared with the control animals, the alcohol-exposed animals showed decreased behavioral flexibility when learning new cognitive tasks and were less inhibited when performing a maze test. The adult animals that had been exposed to alcohol were also more resistant than the control group to training designed to inhibit response to alcohol cues. Importantly, the authors found that these behavioral deficits were reversed when the alcohol-exposed animals were given a compound that improves the function of glutamate receptors in the brain.

Brain scans of the adult rats revealed that the volumes of the hippocampus, thalamus, dorsal striatum, and neocortex were smaller, while the hypothalamus was larger in the alcohol-exposed group compared with controls. These brain regions have been implicated in various aspects of cognition and addiction.

Source:

Gass, J.T.; Glen, W.B., Jr.; McGonigal, J.T.; et al. Adolescent alcohol exposure reduces behavioral flexibility, promotes disinhibition, and increases resistance to extinction of ethanol self-administration in adulthood. *Neuropsychopharmacology.* October 2014, 39(11):2570–83. PMID: 24820536. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24820536

FEATURE: *The Intramural Division . . . Continued from page 1*

scientists, postdoctoral or pre-doctoral fellows, and graduate students.

One of these, the Laboratory of Neurogenetics (LNG), studies the inherited factors contributing to people's vulnerability to alcoholism and addiction, as well as related behaviors and psychiatric pathologies. David Goldman, M.D., who has served as Chief of LNG since 1991, values the flexibility that intramural research, as opposed to grant-based research, promotes.

"When you don't have to sell people an attractive package to secure a grant, it allows researchers to try something a little different, a little more risky," says Dr. Goldman. However, NIAAA's Board of Scientific Counselors reviews all intramural research at least every four years and tenure track scientists are reviewed every two years.

DICBR also seeks to facilitate multi-disciplinary work between labs and Institutes. "We collaborate across labs and that gives us access as needed to different tools and types of expertise. In a center like DICBR, we have so many different tools available, you can put together all the different pieces you need," Dr. Goldman says.

For example, LNG collaborates with the NIAAA neuroscience lab and Laboratory of Physiologic Studies (LPS), as well as with labs at the National Institute on Drug Abuse (NIDA), and the National Institute on Mental Health (NIMH).

These unique collaborations facilitate the kinds of programs Dr. Goldman believes are key to his lab's success. Specifically, he says an emphasis on the "big data" of genomics and on functional genetics allow for exceptional types of discoveries.

"By sequencing genes, large parts of the genome, and genomes, we can identify genetic variants that influence alcohol use disorders and alcohol related behaviors in humans and animal models," explains Dr. Goldman, "and then build on those discoveries."

Collaborations like these are a priority for the Collaborative Research on Addiction at NIH (CRAN) program, the trans-NIH substance use, abuse, and addiction functional integration initiative formally established by NIH Director Dr. Francis Collins in 2012. NIAAA, along with NIDA and NCI, is a primary contributor to this initiative.

Continued on page 6

NOTEWORTHY

FALK LOHOFF JOINS NIAAA AS AN NIH LASKER CLINICAL RESEARCH SCHOLAR

On December 15, the National Institutes of Health (NIH) announced the recruitment of Falk W. Lohoff, M.D., and two other investigators as Lasker Clinical Research Scholars. Dr. Lohoff joined NIAAA as chief of the Section on Clinical Genomics and Experimental Therapeutics in NIAAA's Laboratory of Clinical and Translational Studies, part of the Division of Intramural Clinical and Biological Research.

The Lasker Clinical Research Scholars program at NIH is a joint initiative with the Albert and Mary Lasker Foundation to nurture the next generation of outstanding clinical scientists. This highly competitive program provides talented early-stage researchers the opportunity to carry out independent clinical and translational research for 5 to 7 years at the NIH campus in Bethesda, Maryland. The researchers also have the possibility of additional years of financial support, at NIH or an NIH-funded research institution, upon project review.

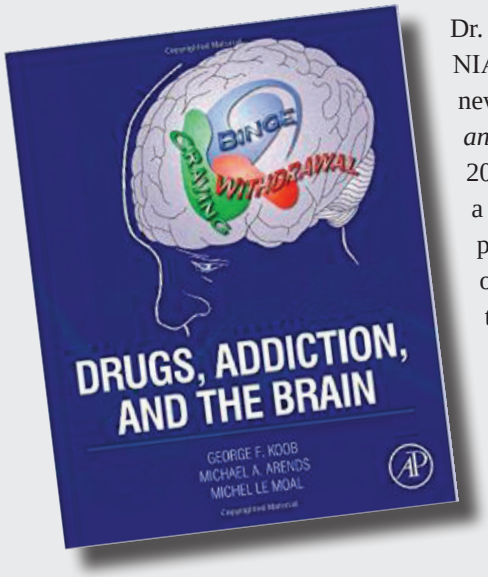
In a news release, NIH Director Francis S. Collins, M.D., Ph.D. said, "Identifying talented and innovative scholars early in their careers is paramount to building a robust cadre of physician-researchers. We hope this continued effort with the Lasker Foundation leads to major scientific discoveries that impact human health."

Dr. Lohoff's research focuses on heritable and non-heritable genetic aspects that influence the onset, progression, and treatment of alcohol use disorders and addictions. Findings from these studies are translated into human clinical studies using diverse approaches, including molecular biomarkers, pharmacogenetics, epigenetics and functional imaging genetics.

Dr. Lohoff received his medical degree from Humboldt University of Berlin in 2002, and completed residency training in psychiatry and a fellowship in neuropsychopharmacology at the University of Pennsylvania. He served as Assistant Professor of Psychiatry at the University of Pennsylvania from 2007–2014.

NOTEWORTHY

NIAAA DIRECTOR AUTHORS TEXTBOOK ON ADDICTION



Dr. George Koob, Director of NIAAA, is the first author on the new textbook *Drugs, Addiction, and the Brain* (Elsevier, 2014). The book provides a detailed overview of the pathophysiology of the disease of addiction by exploring the molecular, cellular, and neurocircuitry systems in the brain that are responsible for drug addiction. Common neurobiological elements are emphasized that provide novel insights into how the brain mediates the acute rewarding effects of drugs of abuse and how it changes during the transition from initial drug use to compulsive drug use and addiction.

NOTEWORTHY

CRAN GRANTS WILL EXPLORE USING SOCIAL MEDIA TO BETTER UNDERSTAND, PREVENT, AND TREAT SUBSTANCE USE

The National Institutes of Health (NIH) has awarded eleven grants to explore the use of social media to advance the understanding, prevention, and treatment of substance use and addiction. The research, which will total more than $11 million over three years, is funded through the Collaborative Research on Addiction at NIH (CRAN), an initiative that comprises the National Institute on Alcohol Abuse and Alcoholism (NIAAA), the National Institute on Drug Abuse (NIDA), and the National Cancer Institute (NCI).

CRAN was established to integrate resources and expertise to advance research and improve public health outcomes related to the use of alcohol, tobacco, and other addictive substances. These new grants are among the first projects supported directly through CRAN.

Facebook, Twitter, Instagram, and other online interactive media have become increasingly important as sources of public information. NIH hopes to learn more about how these technologies affect interpersonal communications and knowledge about substance use.

"The ubiquity and widespread use of social media underscores the need to address questions regarding the intersection of social media with substance use and misuse, with an ultimate focus on its potential as a tool for preventing and treating substance abuse problems," said NIAAA Director Dr. George Koob. "With these awards the CRAN collaboration is making an important investment that could impact the diverse health problems associated with the misuse of alcohol, tobacco, and other addictive substances."

The NIAAA grant recipients are Dr. Yong Ge of the University of North Carolina at Charlotte, who will use data mining techniques to extract tweets related to alcohol and substance use (NIAAA grant AA023975); and Dr. Scott Ian Vrieze, of the University of Colorado, Boulder, who will explore social media involvement and substance use development in adolescent twins (NIAAA grant AA023974).

For descriptions of each project, visit http://addictionresearch.nih.gov/research-portfolio-cran-funded. For more information about CRAN, go to http://addictionresearch.nih.gov.

FEATURE: *The Intramural Division. . .* *Continued from page 4*

"The CRAN structure is often better able to address the issues of addiction in general," said Dr. Kunos. "It allows for economies of scale in our intramural program—we're sharing resources so we can do things even in tight budget times that we wouldn't otherwise be able to do."

Other DICBR collaborative programs with NIDA include a shared institutional review board (IRB) for all human research protocols, a joint center in addictions genomics, and a joint section on clinical psychoneuroendocrinology and neuropsychopharmacology, which runs translational and clinical studies on human patients to identify possible novel medications for addiction. There is also a joint optogenetic core that develops state-of-the art tools to study brain neuronal function in vivo, and a joint medicinal chemistry core that can synthesize and provide chemical substances if research requires it. In addition, about three years ago, Dr. Goldman and Dr. Kunos developed a joint scientific review committee with NIDA that scores every new NIAAA and NIDA human protocol for merit.

Over the years, NIAAA's intramural program has produced numerous significant advances that are recognized across the alcohol research field. For example, Dr. Andrew Holmes' laboratory of Behavioral and Genomic Neuroscience recently published a study in *Molecular Psychiatry* demonstrating a potential therapeutic approach for post-traumatic stress disorder. This approach is based on the lab's discovery that endocannabinoids in the amygdala region of the brain play a role in the extinction of aversive or unpleasant memories. Drs. David Lovinger, Rui Costa, and Steven Vogel published a high profile paper in *Nature* that introduced a novel technique to study the interaction among different neurons in freely moving and behaving mice.

In fact, the number of articles that DICBR contributes to the esteemed *Nature* series of journals testifies to its scientific reputation. Relative to our size, NIAAA would need to publish two and a half papers in *Nature* journals to support NIH's overall ranking. "In 2013, we had eight papers published, so we are doing more than our fair share to contribute to NIH's reputation," explained Dr. Kunos.

DICBR's contribution to NIH's reputation is also reflected in the number of prestigious awards that DICBR scientists have earned. Dr. Holmes recently received the Society for Neuroscience's

Continued on page 8

5 QUESTIONS WITH . . .

GEORGE KUNOS, M.D., PH.D.

Director, NIAAA's Division of Intramural Clinical and Biomedical Research (DICBR)

1 Why is DICBR's work such an important part of NIAAA and alcohol research in general?

It has been my goal in building the intramural program over the last 15 years to staff DICBR with investigators who are recognized leaders in their respective fields (for example, neuroscience, genetics, liver biology, biochemistry, etc.), and who have a keen interest in the biology of ethanol, alcoholism, and comorbid disorders. I believe we have achieved that, as indicated by the quality and impact of the work published by our investigators and the number of awards received and invited keynote lectures given at national and international conferences. Another goal is to focus on innovative approaches that complement rather than compete with extramural investigators. One example is the bench-to-bedside awards, which take advantage of the unique environment of NIH's Clinical Research Center to rapidly move promising findings in our program from the preclinical phase to testing in human subjects with alcohol use disorders. Another example is the UO1 grant mechanism that supports collaborative projects between intramural and extramural investigators, and DICBR has been involved in a dozen or so such studies.

2 You have many laboratories in your division. How do you manage them all while still maintaining an overall vision for DICBR?

No single individual can be an expert in all the different fields of biology our investigators are working in. I see my role as following the many interesting lines of research in our intramural laboratories and facilitating collaborations when I notice complementary aspects in the work of different labs, including my own. Although this requires time and "mental" energy, I benefitted immensely by learning from the insights of my intramural colleagues. Overall, we have a very collegial and interactive group in our program.

3 How has intramural research evolved over the years?

Over the last decade, the intramural program has made important breakthroughs in both molecular and behavioral neuroscience, often through the collaborative efforts of our researchers. Such advances include the development of an innovative approach to monitoring neuronal activity in specific brain regions in freely moving and behaving mice, recently published in *Nature* and *Nature Protocols*. Research from the intramural program has also helped to identify genes that may influence alcohol dependence. Collaboration among senior investigators uncovered the role of the gene, *metabotropic glutamate receptor 2*, in alcohol preference by studying a strain of alcohol preferring rats. Intramural research has also increased understanding about the role of endocannabinoids in alcohol drinking behavior, as well as in alcoholic liver disease, and led to the development of novel, peripheral CB1 receptor antagonists as potential treatment for obesity/diabetes and its complications. The endocannabinoid system in the amygdala has also been identified as a potential therapeutic target for post-traumatic stress disorder. Other advances include work highlighting the potential role of the hormone ghrelin in alcohol craving in human subjects, and the therapeutic potential of interleukin-22 in animal models of alcoholic and non-alcoholic liver disease and fibrosis. Through NIAAA's intramural research, we have also discovered the role of presynaptic glycine receptors in a rare genetic disorder of the central nervous system and the potential therapeutic value of non-psychoactive cannabinoids.

4 What current projects are you particularly excited about and why?

In my own laboratory we found that peripheral CB1 cannabinoid receptors are potential therapeutic targets not only for obesity and diabetes and their complications but, unexpectedly, also for excessive alcohol drinking. We are excited about exploring the underlying mechanisms and even more excited about the future prospect of testing this in alcoholic human subjects using the peripherally selective CB1 inhibitors introduced by our group.

5 You were born and raised in Hungary. What brought you to the United States and to NIAAA?

Although I was born, raised, and earned my medical degree in Hungary, at the time I was recruited to NIAAA, I was Professor of Pharmacology and Medicine at McGill University in

Continued on page 8

FEATURE: *The Intramural Division. . . Continued from page 6*

Waletzky Award for excellent research in neuroscience and substance abuse. He also received the Bennett Award from the Society of Biological Psychiatry for his basic research.

Dr. Lovinger received an NIH Director's Award for "discovering novel forms of synaptic plasticity, providing outstanding leadership in the neuroscience of addiction, and demonstrating exemplary skills as a mentor."

And, Drs. Pal Pacher and Kunos were both selected as Thomson Reuters Highly Cited Researchers in Pharmacology/Toxicology based on highly cited papers published between 2002 and 2012. Furthermore, last year, research by six different DICBR scientists was cited 1,000 or more times in the scientific literature and was published in the top ranking journals.

All told, NIAAA's robust intramural research program, under the leadership of Dr. Kunos, has made significant progress in clinical and basic research, and continues to complement the work of the extramural scientists we support around the world.

FIVE QUESTIONS. . . *Continued from page 7*

Montreal, Canada, where I had received my Ph.D. in pharmacology and stayed on as a faculty member. What brought me to NIAAA is best described by a conversation at the time of my recruitment to NIH with my older daughter (who decided to stay in Canada). She told me she understood why I left Hungary for the better conditions in Canada to pursue a research career, but then she asked what was wrong with Canada? Of course nothing was wrong with Canada and McGill is a wonderful university, but when I received the offer to join NIH, I likened myself to an opera singer who gets an offer to join the Metropolitan Opera. Few singers, if any, have turned down such an offer.

For more information on alcohol use disorders and to assess your own drinking pattern, visit NIAAA's* Rethinking Drinking *Web site.

RethinkingDrinking.niaaa.nih.gov

ABOUT US

NIAAA Spectrum is NIAAA's Webzine. With engaging feature articles, short news updates, and colorful graphics, *NIAAA Spectrum* offers accessible and relevant information on NIAAA and the alcohol research field for a wide range of audiences.

Each issue includes feature-length stories, new research findings from the field, image and data analyses, and an interview with an NIAAA staff member or alcohol researcher. *NIAAA Spectrum* is published three times a year.

CONTACT US

National Institute on Alcohol Abuse and Alcoholism (NIAAA)

5635 Fishers Lane, MSC 9304
Bethesda, MD 20892–9304
Communications/Public Info:
301–443–3860
http://www.spectrum.niaaa.nih.gov

National Institute on Alcohol Abuse and Alcoholism