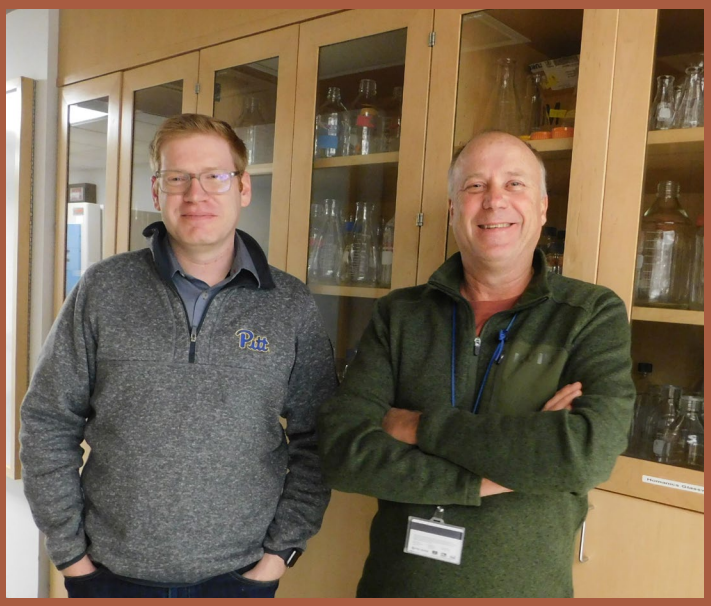
A Closer Look at the Laboratories of
Drs. Sean Farris and Gregg Homanics



Dr. Sean Farris (L) and Dr. Gregg Homanics (R)

How do alcohol and other drugs of abuse affect the brain? Can these substances and related behavior change the way our genes work to cause diseases? Could some of our genes that don't encode proteins play a key role in some of these mechanisms? Drs. Homanics and Farris investigate mysteries such as these in neighboring lab space on the 6th floor of Biomedical Science Tower 3.

Excessive alcohol consumption remains a serious societal problem, with significant economic costs and detrimental consequences to human health. Binge and heavy drinking lead to short- and long-term health risks, including accidents, violence, risky behaviors, mental health issues, cancers, cardiovascular diseases, and gastrointestinal problems. Excessive drinking also increases one's chances of developing alcohol use disorder (AUD), which encompasses alcohol abuse, dependence, and addiction. Department researchers Dr. Gregg Homanics and Dr. Sean Farris study AUD from various angles.

Dr. Homanics' long-term goal is to understand the molecular effects of alcohol on the body so that safe, effective treatments for AUD can be developed. "We want to understand how alcohol affects the brain – that's the bottom line," he explains. "Because once we can understand that, then we may be able to develop treatments for AUD. Remarkably, we don't know how alcohol brings about its effects in the brain." Dr. Homanics is currently Director of the Genetically Engineered Rodent Core and Scientific Co-Director for the Integrative Neuroscience Initiative on Alcoholism (INIA)-Neuroimmune Consortium, a multi-institutional, international group of National Institutes of Health-funded alcohol researchers.

The Homanics lab also studies the intergenerational effects of alcoholism, a genetic disease known to run in families. Two heredity models explain how traits are passed from parents to offspring. "Hard inheritance" explains that traits are passed from parent to offspring though unaltered DNA. The Homanics lab challenges this model by also focusing on "soft inheritance" – the opposing explanation that traits parents acquire during their lifetime can change how genes function, which subsequently allows those traits to be passed to offspring. The lab is currently testing the hypothesis that alcohol exposure produces long-lasting "soft" effects that can be passed down through generations and ultimately impact alcohol drinking and behavioral responses to alcohol. They recently found that paternal preconception alcohol exposure impacts male offspring's behavioral sensitivity to alcohol, alcohol drinking behavior, and response to stress.

Dr. Farris, who is also a member of the INIA Neuroimmune Consortium, joined our faculty in 2020 as an independent, tenure track investigator after completing a postdoctoral research fellowship at the Waggoner Center for Alcohol and Addiction, the Institute for Neuroscience, and the Institute for Cell & Molecular Biology at the University of Texas at Austin. The overarching goal of his research is to identify new mechanisms that contribute to disease, whether it be AUD, addiction to other abused drugs, pain, or other neuropsychiatric disorders. "My research, more broadly, is aimed at epigenetic mechanisms that contribute to disease," Dr. Farris explains. "What are the underlying mechanisms? And what distinguishes the mechanisms of something like pain from the mechanisms behind opiates or schizophrenia?"

The Homanics lab team (L to R): Gregg Homanics, Amit Seth, Carolyn Ferguson, Anna Baratta, and Sonja Plasil

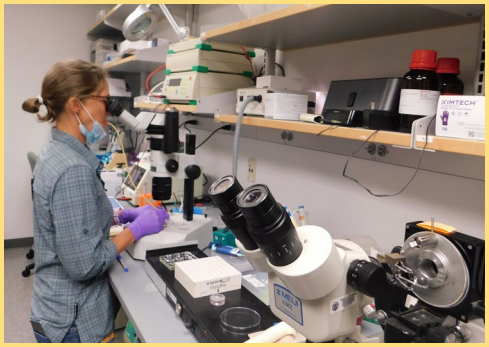
The Farris lab team: (L to R) Adam Bradner, Sean Farris, and Rachel Rice

As part of the INIA consortium, Dr. Farris continues to collaborate on the study "Alcohol-Related Changes in Gene Expression and Structure Using Next Generation Sequencing" with principal investigator (PI) Dayne Mayfield, PhD, from the University of Texas at Austin that started as part of his postdoctoral fellowship work. Drs. Mayfield and Farris propose that alcohol-induced changes in brain function are caused by changes in gene expression and explore these expression changes in humans and different animal species. They also use data from those investigations to predict which medications from existing FDA-approved drugs would work best against AUD. The most promising drugs will then be tested in humans with AUD. So far, they have seen changes in genes related to the drug gabapentin, a medication used primarily to treat neuropathic pain that has been shown in some human lab studies to reduce alcohol consumption. Dr. Farris is also starting a new project in collaboration with the lab of fellow department researcher Bradley K. Taylor, PhD, looking at how chronic alcohol use causes co-morbid pain.

An exciting research focus for both Drs. Farris and Homanics is how alcohol changes genetic factors in the brain, including non-coding RNA (ncRNA) and long ncRNA (lncRNA), and how those changes are related to AUD. Dr. Homanics explains: "DNA is the blueprint of life. Some of our genes make proteins. And that's what everybody has focused on for the past couple decades. It turns out, only a very small part of the genome makes proteins. The vast majority of the genome makes these ncRNAs, and everybody's ignored them for years. But they are there for a reason. I think they're really important." Dr. Farris elaborates: "To date, their functions are largely unknown, but we're finding out that they are very cell type- and tissue-specific and they play key roles in regulating gene expression, particularly in disease states."

Dr. Homanics studies lncRNAs as PI on the project "Role of Noncoding RNA in Alcohol Action" for the INIA consortium. He hypothesizes that individual lncRNAs are key regulators of ethanol drinking. The Homanics lab produces and analyzes genetically-engineered animals with altered lncRNA expression, first screening these mutant animals for changes in ethanol drinking and then observing animals with altered drinking behavior for insights into the mechanisms behind the behavior, including molecular, transcriptomic, cellular, and additional behavioral investigations.

First-year graduate students Rachel Rice (L, Homanics lab/Farris lab) and Adam Bradner (R, Farris lab) preparing samples using gel electrophoresis to analyze genetic mutations.



Carolyn Ferguson (Homanics lab manager for the past ~25 years) prepares single cell embryos to create novel, genetically-engineered mice.

Sonja Plasil (L, Homanics lab) and Richa Rathod (R, Farris lab) gathering and preparing different cell-types and brain samples for analysis.

Dr. Farris studies lncRNAs as well, as PI on the National Institute on Alcohol Abuse and Alcoholism-funded study "Long Non-Coding RNA Regulation of Alcohol Drinking Behavior." In this project, Dr. Farris uses computational biology, state-of-the-art sequencing, and focused gene-targeting approaches to study the neurobiology of chronic alcohol abuse, which may lead to improved gene-based diagnostics and treatment options for AUD. Identifying and testing the biological role of lncRNAs in the context of the brain and alcohol drinking behavior could potentially lead to an improved understanding of disease and new pharmacotherapies.

Both Dr. Homanics' and Dr. Farris' work extends beyond AUD other diseases. The Homanics lab genetically engineers rodents and non-human primates used not only in their own studies, but also in studies by collaborators all over the world on human diseases like Angelman syndrome, maple syrup urine disease, and Alzheimer's disease. Dr. Farris is working on a new project looking at general ncRNA mechanisms and investigating enigmas such as the fundamental functions of lncRNAs in the brain, rather than their role in a specific disease like AUD. "Since most of them have never been studied before, we're trying to be trailblazers, in a sense, to figure out what these unannotated genes do. Nobody knows what they are. We're just trying to understand them on a very fundamental, basic science, basic biology level," says Dr. Farris.

Both Drs. Homanics and Farris agree that the study of non-coding genes is a very critical area of focus for future projects, such as trying to find medications that actually work via these genes. All medication development to date has been focused on protein-coding genes, which comprise less than 2% of our genome. The rest of our genetic code is made up of non-coding genes. "Could we, in the long term, design medications that would work through non-coding genes rather than protein-coding genes?" asks Dr. Farris. Investigations by the Homanics lab and the Farris lab could indeed lead to exciting innovations in drug design and pharmacogenomics.

Homanics Lab Key Publications

Rompala GR, Mounier A, Wolfe CM, Lin Q, Lefterov I, **Homanics GE**. Heavy Chronic Intermittent Ethanol Exposure Alters Small Noncoding RNAs in Mouse Sperm and Epididymosomes. Front Genet. 2018 Feb 8;9:32.

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Finegersh A, **Homanics GE**. Paternal alcohol exposure reduces alcohol drinking and increases behavioral sensitivity to alcohol selectively in male offspring. PLoS One. 2014 Jun 4;9(6):e99078.

Chandra D, Jia F, Liang J, Peng Z, Suryanarayanan A, Werner DF, Spigelman I, Houser CR, Olsen RW, Harrison NL, **Homanics GE**. GABAA receptor alpha 4 subunits mediate extrasynaptic inhibition in thalamus and dentate gyrus and the action of gaboxadol. Proc Natl Acad Sci U S A. 2006 Oct 10;103(41):15230-5.

Mihalek RM, Banerjee PK, Korpi ER, Quinlan JJ, Firestone LL, Mi ZP, Lagenaur C, Tretter V, Sieghart W, Anagnostaras SG, Sage JR, Fanselow MS, Guidotti A, Spigelman I, Li Z, DeLorey TM, Olsen RW, **Homanics GE**. Attenuated sensitivity to neuroactive steroids in gamma-aminobutyrate type A receptor delta subunit knockout mice. Proc Natl Acad Sci U S A. 1999 Oct 26;96(22):12905-10.

Farris Lab Key Publications

Farris SP, Mayfield RD. Epigenetic and non-coding regulation of alcohol abuse and addiction. Int Rev Neurobiol. 2021;156:63-86. Epub 2020 Oct 14.

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Farris SP, Tiwari GR, Ponomareva O, Lopez MF, Mayfield RD, Becker HC. Transcriptome Analysis of Alcohol Drinking in Non-Dependent and Dependent Mice Following Repeated Cycles of Forced Swim Stress Exposure. Brain Sci. 2020 May 2;10(5):275.