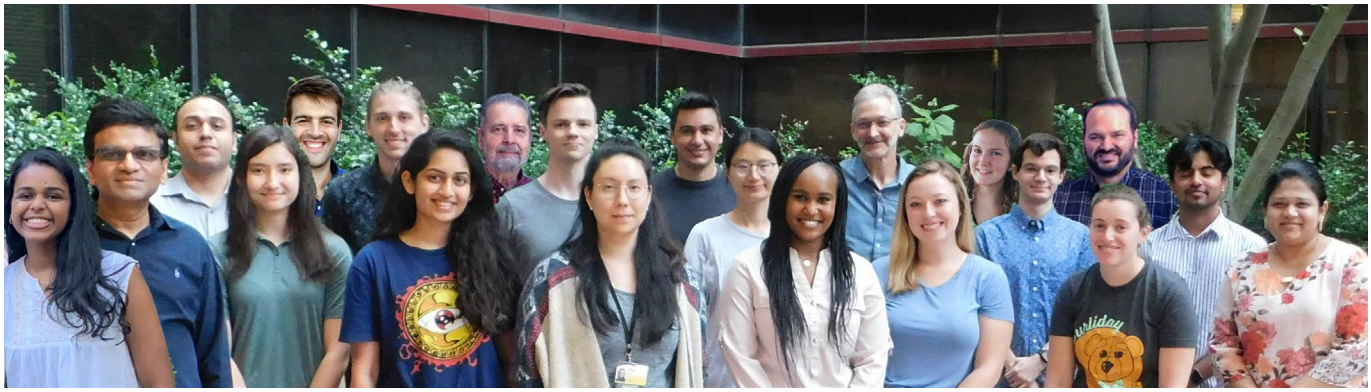
A Closer Look at the Laboratory of **Dr. Bradley Taylor**

On the 13th and 14th floor of Pitt's Biomedical Science Tower (BST), Professor Bradley K. Taylor, PhD, and his research team are searching for the answers to some very important questions about pain. Questions like: How does the body control its own pain? How does short term pain develop into long-term pain? Can existing drugs be repurposed to treat pain?



The Taylor Lab Research Team

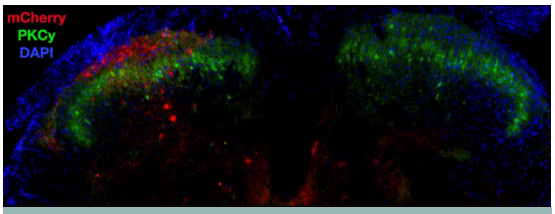
Dr. Brad Taylor, who joined our department in 2018, has made a considerable impact in the field of chronic pain research. His National Institutes of Health (NIH)-funded research laboratory discovers, visualizes, and manipulates pathological changes in brain and spinal circuits that develop in the setting of traumatic injury. His laboratory is closely affiliated with the Pittsburgh Center for Pain Research, a collaborative environment with core investigators in the Department of Anesthesiology & Perioperative Medicine and the Department of Neurobiology.

A major goal of Dr. Taylor's team is to understand our body's endogenous (natural) pain control systems. At their best, opioid receptors can provide long-term relief from postoperative pain, but at their worst, they may contribute to the transition from acute to chronic pain after surgery. "What we believe is that surgery recruits two opposing systems in the spinal cord and perhaps the brain as well – one that promotes pain sensitization and one the promotes pain inhibition. The sensitization – referred to as latent sensitization - is kept at bay by a powerful endogenous opioid receptor system. This opioid system tunes the pain to a level that is appropriate to the situation," explains Dr. Taylor. In other words, when pain is needed to protect us from additional tissue damage, sensitization is high and endogenous pain inhibition remains low. If we experience pain that is more than protective, then the opioid receptor system can kick in and dampen it. Remarkably, data from the Taylor lab indicates that, once turned on, these opposing systems can remain on for months, if not years. "The problem is," continues Dr. Taylor, "any dysfunction of the opioid receptors in the ensuing weeks, months, or years after a surgery could lead to a transition to a chronic pain state."

Currently, the Taylor lab conducts this research using mouse models. For example, an incision to the hindpaw and the underlying muscle leads to a short-lasting sensitivity of the skin to touch, just as is observed in the postoperative patient. To study latent sensitization and the vulnerability to developing chronic pain, the mice can be challenged with the drug naltrexone. Naltrexone blocks the endogenous opioid receptor system, leading to a robust reinstatement of the cutaneous hypersensitivity. Hundreds of these animals can be housed in a somewhat unique facility in the BST that provides the research team with the ability to conduct long-term studies of chronic pain using state-of-the-art live animal imaging and recording technologies, including GCaMP calcium imaging as well as behavioral pharmacology in cre-transgenic mice using optogenetics and chemogenetics – work that is not available in conventional animal facilities.

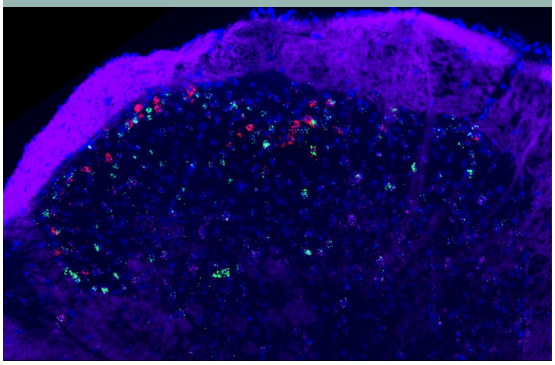
Remarkably, the Taylor laboratory reported that naltrexone not only reinstated skin hypersensitivity, but also produced behavioral signs of opioid withdrawal, analogous to what happens to an opioid drug-dependent patient who abruptly stops receiving the drug. Dr. Taylor elaborates: "We think that this endogenous opioid receptor activity not only provides analgesia that silences the latent sensitization, but also leads to dependence. Our lab is continuing to study this 'endogenous opioid receptor dependence' – it's a term that we coined…we think that understanding endogenous dependence will help us understand the mechanisms of dependence to addictive narcotics. Such links between

L: Christopher Norris performs high resolution, *in vivo* live calcium imaging of mouse spinal cord slices; R: Chris observes a wave form image of a population of activated neurons on the slide.



Top: The Taylor lab utilizes modern advents in viral and genetic technology to selectively label spinal cord dorsal horn interneuron populations (shown in red mCherry labeling). This precision allows the selective activation and inhibition of distinct neural populations during naïve and pain behavioral testing to probe the neurobiological underpinnings of chronic pain.

Bottom: Another commonly utilized research method in the Taylor lab is multi-label fluorescence in situ hybridization (FISH). This technology allows researchers to visualize and map the mRNA in individual cells to help define gene expression in individual neuron populations or to assess temporal and spatial gene expression changes during acute and chronic pain. Images courtesy of Tyler S. Nelson.



mechanisms of chronic pain and opioid dependence are relevant to the current opioid epidemic." Some of Dr. Taylor's work in this area is funded by the NIH Helping to End Addiction Long-term, or the NIH HEAL Initiative, in response to Congress' mandated expenditure of $500 million a year over at least five years to help deal with the national opioid crisis. It's been importantly recognized that pain plays a major role in this opioid crisis. "How do people get exposed to opioids in the first place? Because they have the legitimate complaint of pain," Dr. Taylor points out. "But problems occur when patients are prescribed more than a couple of days of opioids for postoperative pain." These problems include opioid diversion and misuse (the latter word replacing "abuse" and "addiction"), to which some people are genetically prone.

Dr. Taylor stresses the importance of recognizing the difference between dependence and misuse/addiction. "Dependence is not necessarily bad. It just means that continued opioid use is necessary to prevent the occurrence of withdrawal symptoms. I'm not as concerned with opioid use in patients who have become dependent by achieving pain control due to terminal cancer or are in end-of-life hospice care. More importantly, misuse can lead to addictive behaviors that are devastating to life, well-being, and relationships with other people. These behaviors include stealing from family to buy more drugs. This distinction between dependence and misuse is too often lost and contributes to a damaging societal stigma attached to any form of opioid use, including beneficial uses to treat really severe acute pain or terminal chronic cancer pain."

With a new initiative that's in the early stages of development - the Pittsburgh Project to End Opioid Misuse (PPOM) -- the Taylor lab continues to expand its human subjects research program. The project will unite researchers from throughout Pitt, UPMC, and other and neighboring research hospitals who are interested in studying the intersection between chronic pain and opioid misuse. Collaborators will come from a wide variety of medical disciplines like psychology, psychiatry, anesthesiology, obstetrics, and internal medicine. "It's one of the exciting aspects of the center – it will cross interdisciplinary boundaries and help break down silos, with researchers interacting even more" says Dr. Taylor. Dr. Taylor explains that one of the major risks for surgery is the possibility of tissue injury that can lead not only to acute pain, but also chronic post-operative pain, in double-digit percentages. "We're interested in the mechanisms of the transition from acute pain to chronic post-operative pain." The Taylor lab is teaming up with clinical investigators at UPMC Magee-Womens Hospital, including Grace Lim, MD, MS (Dept. of Anesthesiology & Perioperative Medicine) and Emilia J. Diego, MD (Dept. of Surgery), to determine whether there's still latent sensitization that is being masked by the opioid receptor system in human patients after mastectomy. They will test their sensory thresholds, give them naloxone to block the opioid receptor system, and then test again to see whether their sensitivity to touch or to heat or to cold increases. An increase would reveal latent sensitization and could even represent a biomarker for vulnerability for the development of chronic pain. So far, results using human experimental models of pain from Dr. Taylor's collaborators in Denmark have been promising. "We've teamed up with a group led by Mads Werner at the University of Copenhagen to do clinical trials, and we look forward to continuing those studies in Pittsburgh."

Another key goal of the lab's research program is to develop new analgesic drugs for the treatment of chronic pain due to inflammation or in the setting of neuronal injury, diabetes, or multiple sclerosis (MS). Chronic pain is quite common, but the impact of available treatments is small to moderate at best. A new pharmacotherapy is desperately needed. One fast-track strategy is to repurpose a drug that is already FDA-approved for another disease. The first focuses on a class of drugs used to control diabetes often referred to as glitazones. The Taylor lab discovered that the receptors for these drugs (PPAR) are localized not only in the pancreas and other areas important in metabolism, but also in the dorsal horn of the spinal cord, which is important for pain modulation. When given to animals, they found that pioglitazone (trade name Actos) produced big reductions in behavioral and molecular signs of chronic pain in rat models of traumatic nerve injury or painful diabetic neuropathy. The second drug focuses on fingolimod (trade name Gilenya), a relatively new drug used to treat MS. The Taylor lab found that fingolimod acts at sphingosine-1-phosphate

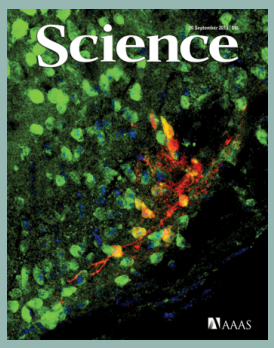
L: Nina Gakii slices sections of mouse spinal cord.

R: Ron Sivak conducting PCR to genotype transgenic mice.

receptors to alleviate chronic pain-like symptoms in an animal model of MS. These studies pave the way for clinical trials to determine whether pioglitazone and fingolimod can be repurposed for the treatment of chronic pain conditions. "Furthermore," Dr. Taylor explains, "about half of MS patients experience severe pain, and it's about the same for patients with advanced diabetes. So not only could we repurpose these drugs for other types of pain, we could also emphasize the use of these drugs for the disease state that they were developed for." He emphasizes the advantages of using just one drug to treat two major symptoms of disease, with pioglitazone becoming the optimal choice for patients with diabetes and diabetes-related pain, and fingolimod for patients with MS and MS-related pain: the avoidance of adverse effects associated with opioids and other painkillers.

Dr. Taylor leads a research team of over 18 people, including two research assistant professors, six postdoctoral fellows, three staff associates, two PhD candidates, and five Pitt undergraduate students. He attests that working with the people in the "TLAB" is what he enjoys most about his work. "I address them as 'colleagues,' because we're really in this together as a team, sharing ideas, planning and strategizing resources, troubleshooting problems, making cool discoveries. Mentoring others and watching them grow is very satisfying and rewarding," says Dr. Taylor. His mentoring philosophy includes immersion in a research-intensive environment focused on translational pain research, development of oral and written communication skills, acquisition of powerful experimental techniques, and exposure to a rich educational environment and guidance for the development and achievement of long-term goals. He has directed significant laboratory research projects of over 70 learners, including 20 early career assistant professors, anesthesiology medical residents, and postdoctoral fellows, many of whom have published in top medical research journals and received NIH funding and tenure-track positions in academia. He also asserts that he greatly enjoys working with collaborators, who in addition to interdisciplinary colleagues at Pitt, include investigators at Indiana University Medical School, University of Alberta, University of Copenhagen, Karolinska Institute, University of Glasgow, University of Heidelberg, UCLA, University of Minnesota, University of Kentucky, Emory University, Johns Hopkins University, and the University of Texas Medical Branch.

Key Publications



Dr. Taylor's 2013 *Science* article (Constitutive μ-opioid receptor activity leads to long-term endogenous analgesia and dependence. Science. 2013 Sep 20;341(6152):1394-9) was a landmark achievement. Not only was the work published in one of the world's top academic journals, it was also featured on the cover of the journal and received substantial media coverage including *Businessweek*, *New Scientist*, *Nature blog*, and *Pain Research Forum*.

Solway B, Bose S, Corder G, Donahue R, **Taylor BK**. Tonic inhibition of chronic pain by Neuropeptide Y. Proceedings of the National Academy of Sciences 108:7224-9 (2011). PMC3084123

Griggs RB, Donahue RR, Morgenweck J, Grace PM, Sutton A, Watkins LR, **Taylor BK**. Pioglitazone rapidly reduces neuropathic pain through astrocyte and nongenomic PPARg mechanisms. Pain 156:469-82 (2015). PMC4329091.

Griggs RB, Santos DF, Laird DE, Doolen S, Donahue RR, Wessel CR, Fu W, Sinha GP, Wang P, Zhou J, Brings S, Fleming T, Nawroth PP, Susuki K, **Taylor BK**. Methylglyoxal and a spinal TRPA1-AC1-Epac cascade facilitate pain in the db/db mouse model of type 2 diabetes. Neurobiology of Disease 127:76-86 (2019). PMC6776480

Nelson TS, **Taylor BK**. Targeting spinal neuropeptide Y1 receptor-expressing interneurons to alleviate chronic pain and itch. Progress in Neurobiology Aug 7 doi:10.1016/j.pneurobio.2020.101894 (2020). PMID32777329