



# The Stucky Lab

**Dr Cheryl Stucky** offers an insight into the work of her laboratory at the Medical College of Wisconsin, and explains how their studies are offering a superior insight into the underlying mechanisms of pain

**Can you describe your research into the Transient Receptor Potential ion channel family? What are these proteins and what role do they play in sensory neurobiology?**

The Transient Receptor Potential (TRP) ion channels are a class of molecular sensors for temperature, chemicals and touch stimuli. These ion channels sit in the membrane of sensory neurons and are essential for the initial transduction of sensory stimuli into generator potentials and, subsequently, action potential signals that are sent to the spinal cord. Some of the more well-known TRP channels that are found in mammals, including humans, are from the TRPV, TRPM and TRPA1 families. The TRPV1 (Vanilloid) receptor is the receptor for capsaicin, the hot ingredient in chili peppers, and is also a key receptor for the hypersensitivity to heat stimuli that occurs after tissue inflammation such as a sunburn or skin infection.

**What are the greatest challenges that you have encountered through your investigations into sensory neurobiology and mechanical receptors?**

The biggest challenge for the field of mechanotransduction in sensory neurons is that the proteins that underlie mechanotransduction are elusive and difficult to identify. The receptor endings of these neurons are extremely small and diffusely expressed in the skin throughout the body. Furthermore, there are likely to be multiple proteins in complicated complexes and redundant processes that ultimately contribute to mechanotransduction in somatosensory neurons. Moreover, there are a variety of sensory neurons that are tuned to different types of touch stimuli and whether they use similar or different transduction mechanisms is a mystery. All of these issues make it challenging to identify and study the key players in mechanotransduction.

**What role do pharmacological blockers play in your translational studies into touch-evoked**

## pain? What are the main advantages and disadvantages of this technique?

They play a very important role. Foremost, they allow us to acutely inhibit the channel after development, without removing the protein from the membrane. They also avoid the issues of potential compensation from other proteins that can occur when a single gene is deleted in the embryo and throughout development of the animal. When combined with 'pre-clinical' models of pain and injury, the pharmacological tools allow us to predict whether small molecule inhibitors of the channel could be effective in patients with painful conditions associated with tissue injury or disease. However, the disadvantages are that we often do not know the concentration of the inhibitor at the target site of action, and there may be side effects of the compound due to inhibition of channels expressed in sites other than peripheral sensory neurons. Furthermore, compounds that are highly effective in pre-clinical animal models are sometimes ineffective in human patients, either due to a species difference or to the preclinical model not effectively mimicking the injury or disease in human patients. This problem of accurately translating from preclinical animal models to human patients is one of the biggest current challenges for pain researchers today.

## Who have been the most prominent and rewarding partners in your studies? Is effective and efficient collaboration essential to tackling the issue of chronic pain?

I think collaborating with bright and interesting people who work on aspects of science that are different from my area is one of the most rewarding attributes of my career. I truly enjoy the long-term relationships I have built with many other scientists. I have enjoyed a successful collaboration with Cheryl Hillery, MD, a haematologist at the Medical College of Wisconsin, who treats children and adults with sickle cell disease, and who studies vascular effects of sickle cell disease. Dr Hillery and I share an NIH grant together to study pain mechanisms in sickle cell disease. This has been a novel and fruitful collaboration between two experts in very different fields who have come together to study a prevalent but little understood problem. I think this type of collaboration with experts in two diverse areas is absolutely essential to tackling the problem of sickle cell disease pain.

My lab, particularly my MD/PhD student Rick Lennertz, has enjoyed a fruitful collaboration with Dr Diana Bautista, a neuroscientist at University of California, Berkeley. Together we have investigated mechanisms that underlie tingling and numbing paresthesias, such as those elicited by a natural compound called hydroxy-alpha-sanshool which is extracted from Szechuan peppercorns. Dr Bautista's lab focuses more on molecular targets of sanshool, whereas my lab brings the expertise of the physiology and effects of sanshool on different fibre types. Strong collaborations with scientists at Amgen Inc. and Abbott Laboratories have provided novel and selective compounds for study of specific transduction channels.

# No pain, all gain

Since its creation in 1999, **The Stucky Lab** has worked at the forefront of neurobiology, studying the molecules responsible for touch and pain. We explore the function of the laboratory, and its latest research

**THE AVERAGE HUMAN** adult is encased by 22 square feet of skin, acting as a waterproof and insulating shield that helps to guard against the extremes of temperature, harmful sunlight and dangerous chemical agents. Each square foot of skin is pitted with thousands of sensory receptors, meaning that it is fundamental to the way in which we interact with the world around us.

Dr Cheryl Stucky, of The Stucky Laboratory at the Medical College of Wisconsin, has dedicated her life to the study of somatosensory and pain research, investigating how our skin sensory neurons detect environmental stimuli, such as touch and temperature sensation.

## THE STUCKY LAB

Formed in July 1999, The Stucky Lab has sought to understand the role of sensory neuron ion channels and proteins that inform transduction and transmission of sensory stimuli, from simple touch, to pain and temperature. Recently, Stucky has placed a particular emphasis on mechanotransduction mechanisms, the study of the mechanisms by which cells convert mechanical stimuli into chemical activity: "Although we sense tactile stimuli and mechanical pain stimuli on a daily basis, very little is yet known about the molecules and proteins that underlie this sensation," she asserts. "Understanding the mechanisms behind mechanotransduction is really one of the greatest frontiers left in sensory neurobiology. Our laboratory seeks to understand how these channels are modified by injury and disease, and therefore contribute to pathological pain and touch sensitivity."

## A UNIQUE APPROACH

As a postdoctoral fellow with both Martin Koltzenburg and Gary Lewin, Stucky has developed a skin-nerve experimental technique which enables the quantification and recording of responses of single skin sensory neurons to natural stimuli.

The technique involves dissecting a peripheral nerve with the skin it innervates, keeping the nerve and tissue alive for around eight hours in a recording bath. The nerve is then broken down into smaller nerve bundles until the team is able to record from a single functional axon – the part of the nerve cell that transduces and transmits sensory stimuli to the spinal cord. From this they can determine the function of the fibre by locating its receptive field and utilising electrical stimuli to ascertain its conduction speed. They can then apply known amounts of pressure to the receptive field (ie. cold or heat) to measure the number of action potentials that are elicited by the stimulus to the receptive field.

"This method is unique because it gives a very quantitative read out the number of action potentials to known stimuli, and the stimuli are applied to the environment of the sensory terminals as they 'naturally' exist in the skin tissue," declares Stucky.

## AN INNOVATIVE APPLICATION

The unique technique developed by The Stucky Lab has enabled the novel exploration of Transient Receptor Potential Ankyrin 1 (TRPA1), a receptor responsible for hypersensitivity.

Hypersensitivity is a common problem that is related to chronic neuropathic and persistent inflammatory pain. Noxious environmental stimuli are converted into electrical impulses that are then transmitted to, and interpreted by, the central nervous system. In order to treat hypersensitivity, it is essential that the molecular mechanisms that convert noxious information into neural signals are identified, enabling researchers to block both acute and chronic pain responses.

The Stucky Lab has utilised their skin-nerve approach to determine the contribution of TRPA1 to the responses of sensory neurons to touch and pressure on the skin. Using murine

## INTELLIGENCE

### THE STUCKY LAB

#### OBJECTIVES

The Stucky Lab is using transgenic mice and pharmacological blockers in translational studies to determine whether the TRPA1 channel is responsible for touch-evoked pain in several mouse models of chronic pain. These models include mice with severe sickle cell disease, neuropathic (nerve injury) pain, and cancer tumour pain. Over 50 per cent of people suffer from chronic pain at some point in life. Thus, The Stucky Lab is working to provide evidence for the clinical utility of TRPA1 blockers in human patients with chronic touch-induced pain.

#### KEY COLLABORATORS

From Medical College of Wisconsin:

**Cheryl Hillery, MD • Rick Lennertz • Daniel Vilceanu, MD, PhD • Elena Kossyрева • Sheldon Garrison, PhD • Marie Barabas • Andy Weyer • Amanda Smith**

**Diana Bautista, PhD**, University of California, Berkeley

**Donald Simone, PhD**, University of Minnesota

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**CHERYL L STUCKY, PhD**, has studied somatosensory and pain research for the past 20 years. She attained her PhD degree in Neuroscience from the University of Minnesota in 1995, in the laboratory of Dr Virginia Seybold. Next, she moved to Germany where she did a postdoctoral fellowship in the laboratory of Dr Martin Koltzenburg at the University of Würzburg, Germany, followed by a postdoctoral fellowship in the laboratory of Dr Gary Lewin at the the Max Delbrück Center for Molecular Medicine, Berlin, Germany. Since 1999, she has been head of her own lab at the Medical College of Wisconsin.



models that lack the TRPA1 gene, the team has compared the responses of sensory neurons of these mice with normal controls, which demonstrated that TRPA1 is essential for mechanical responses in pain receptors, and in some light touch receptors. To verify this result, Stucky conducted further tests to explore the function of TRPA1: "We did parallel experiments in normal mice where we blocked the TRPA1 channel pharmacologically with a small molecule inhibitor, and analysed the effect of this blockade on mechanical responses," she recalls. "We found very similar results by either pharmacologically, or genetically, inhibiting the TRPA1 channel."

Furthermore, The Stucky Lab was able to demonstrate that, at the sensory membrane, TRPA1 appears to amplify the signal simulated by touch or pressure to another mechanotransducer. "We believe this is a substantial finding in developing our understanding of hypersensitivity and the underlying mechanisms responsible for it," Stucky affirms.

#### CUTTING CHRONIC PAIN

Chronic pain can be a debilitating condition that greatly affects the daily lives of those who suffer from it. The Stucky Lab has recently conducted research into the role of chronic pain in sickle cell disease, where red blood cell sickling leads to excruciating episodes of pain. They found that the pain related to sickle cell disease has been greatly overlooked in previous studies, and that by adulthood many patients experience chronic pain on a daily basis. Furthermore, this disease is highly prevalent in African American and Hispanic populations, which are often greatly underserved by the U.S. healthcare system, further decreasing their quality of life.

Through the use of transgenic mouse models, Stucky found that the mice have chronic pain behaviour related to touch stimuli, as well as cold and heat, and that red blood cell sickling exacerbates the pain. She then investigated the mechanisms that led to this sensitisation by testing antagonists against TRPA1 and transient receptor potential cation channel subfamily V member 1 (TRPV1) receptors. Stucky discovered that inhibition of TRPV1 channels reversed the

mechanical sensitisation at the sensory neuron and behavioural levels.

While this is a recent breakthrough, clinical trials of her findings have already commenced. Thus far they have demonstrated that, while initial TRPV1 antagonist compounds had some success, they caused thermoregulatory side effects and also elevated the heat detection threshold of patients, meaning patients experienced a greater risk of skin burn.

Stucky is optimistic that novel TRPV1 antagonists may be developed that will provide pain relief without these side effects: "Our datasets suggest that future TRPV1-targeted compounds that lack these side effects should be considered for studies in human clinical trials to determine whether they provide safe, effective pain relief for patients suffering from sickle cell disease," she comments.

#### DEDICATION TO REDUCING PAIN

The Stucky lab has served as much more than a place to explore the intricacies of pain induction and response. Indeed, Stucky has also been responsible for providing an atmosphere for young scientists to develop their careers: "I think a really important aspect of my life as a scientist is to make science enjoyable and exciting, and to teach students to love searching for the answers," she enthuses.

Stucky has been able to attract a wealth of young scientific talent to her laboratory and develop a team of young investigators. Their success, and the success of their research into neurobiological pain, can be directly attributed to her positive attitude: "Despite the competitive nature of science, it is important to be kind and generous to colleagues whenever possible, and to consistently mentor and build up young investigators and students".

While Stucky has already achieved much in her career to date, she is determined to continue to explore neurobiological pain, and to find innovative methods for treating pain-related conditions. With her determination, experience and support of her young team, the next breakthrough is surely just around the corner.



THE STUCKY LAB (left to right): Andy Weyer, Rick Lennertz, Sheldon Garrison, PhD, Marie Barabas, Elena Kossyрева, Amanda Smith, and Cheryl Stucky, PhD.