Growing pains

With an early interest in pain modulatory mechanisms and functional pain disorders in humans, Dr Andrea Nackley discusses how her experiences have led her to focus on the importance of translational research in the management of chronic pain.

Could you provide a brief introduction to your research into pain management?

According to Michael Rubinstein, a physicist from the Carolina Virtual Lung Project, “When nature creates something it’s just science - it’s not split into biology, physics, or chemistry. To understand the full complexity of nature one has to break it into parts of the picture and then pull it all back together again.” Breaking down pain into parts of the picture requires collaboration among scientists and clinicians within an enabling infrastructure. By marrying pain neurobiology, behavioural pharmacology, and molecular genetics with clinical epidemiology, my lab hopes to bridge the significant gap existing between basic science and clinical research, in order to better understand the mechanisms underlying maladaptive chronic pain conditions and identify more rational treatment strategies.

How has the focus of your work evolved throughout the course of your career? What are the driving forces that have guided your research?

My research experience began as a graduate student at the University of Georgia, where I studied the role of the cannabinoid CB2 receptor in regulating inflammatory pain. My interest in pain modulatory mechanisms led me to pursue a postdoctoral position at the University of North Carolina, where I investigated human genetic risk factors that contribute to functional pain disorders.

These earlier research experiences were instrumental to my growth and development as an independent investigator in the field of pain, but I spent the majority of my time at the bench, removed from the actual conditions I was trying to understand. Through receipt of a National Institutes of Health (NIH) Roadmap award, I was able to work alongside prominent clinicians to gain training and experience in human pain phenotyping, clinical exams, and clinical epidemiology. Gaining this clinical experience and intelligence evolved the way I think about pain and the way I study it.

What are the main objectives of your study into pain management?

Pain is a multidimensional sensory and emotional experience that is important for our survival, but once pain becomes chronic it is no longer beneficial and, instead, becomes a disorder in and of itself.

There are three main objectives of my research in this area. First, I hope to determine the factors that put some people, but not others, at risk for maladaptive chronic pain conditions. Second, I hope to elucidate the mechanisms whereby genetic, biological, and environmental factors drive chronic pain, a line of inquiry that will provide novel targets for the development of individualised therapeutics for the management of chronic pain. Lastly, I hope to improve pharmacologic management of pain by conducting pre-clinical studies to test new compounds and to optimise the efficacy of existing compounds in patient-relevant animal models.

What have been the biggest successes of your research career to date?

Over the past 15 years I have made several key discoveries regarding pain processes and modulatory mechanisms. These include the identification of human genetic variants associated with chronic pain; determining the molecular mechanism whereby pain-relevant genetic variants lead to functional changes in protein expression and activity, and also the identification of biomarkers such as cytokines, transcription factors and microRNAs, that distinguish individuals with aetiologically distinct manifestations of chronic pain.

My most well-known success has been in the area of catecholamine signaling, where I established a causal role for catechol-0-methyltransferase (or COMT) and beta-adrenergic receptors in the development of pain at the molecular, cellular, and systems level.

Among my more recent successes, I’m most excited about an investigation of chronic pelvic pain that identified clinical features and biological pathways unique to different condition subtypes.

Little is known about the underlying molecular mechanisms of pain conditions. Why is this?

An individual’s pain experience is as unique as their fingerprint - shaped by many factors, including the context surrounding the event, past experiences, stress level, belief systems, coping strategies, and general health. Combine with that, individual variability in genes that regulate the development and function of the nervous system, immune response, and psychological mood, and you can quickly begin to appreciate the complex nature of pain.
Chronic Pain

At the University of North Carolina, Chapel Hill, researchers at the Nackley Lab are providing vital evidence that is beginning to unlock the mysteries of chronic pain.

PAIN IS AN alarm bell, a warning of imminent tissue damage, which rings violently when damage occurs. It also serves as an emergency response call for wound healing and tissue repair. According to the International Association for the Study of Pain, one in five adults is afflicted with a pain that outlasts its stimulus.

Chronic pain can come in multiple forms. Inflammatory pain disorders such as arthritis or post-surgical pain can occur as a response to damage to tissues and infiltration of immune cells, whereas neuropathic pain disorders, like trigeminal neuralgia and sciatica, occur in response to damage of the nerves. Unlike inflammatory and neuropathic pain, idiopathic pain disorders are characterised by perpetual abnormalities in sensory processing that occur in the absence of direct inflammation or nerve damage, making them even more difficult to study.

With therapeutic regimes currently resembling a trial and error approach, the lack of effective, individualised treatment can have severe physiologic, psychologic and socioeconomic consequences, making chronic pain a global problem.

THE AETIOLOGY OF CHRONIC PAIN

Striving to give pain patients better therapeutic choices, Dr Andrea Nackley is leading a research programme that aims to elucidate the causes and improve the pharmacological management of chronic pain. Nackley is an Associate Professor with the University of North Carolina’s Centre for Pain and Research Innovation, holding posts in both the neurobiology and pharmacology departments, where she has been studying chronic pain since 2008.

For Nackley’s research to have a real impact, it is crucial that her results have translational merit. Patient-centred outcomes should always be at the heart of chronic pain management, meaning Nackley employs a bedside-to-bench and bench-to-bedside approach, routinely collaborating with clinicians on projects to guide and test the hypotheses her lab develops.
A major roadblock to improving the management of chronic pain is that the factors predisposing individuals to such disorders are not well understood. Currently, doctors have difficulty administering treatments that are not accompanied by a series of side effects. While two people may share the same diagnosis of chronic pain, their clinical signs and symptoms may be completely different, as Nackley explains. “Patient A may develop temporomandibular disorder following displacement of the anterior disc, while patient B develops the disorder due to the presence of a genetic variant.” Naturally, these patients would benefit from different treatments, but choosing the right one requires an understanding of each individual’s molecular genetic features.

Also problematic is the variance of patient responses to available treatments. What benefits one patient with minimal side effects might provide limited pain relief and substantial side effects for another. To find the most appropriate therapy at an individual level, Nackley’s research aims to uncover the factors that put some individuals at greater risk of developing chronic pain and to identify new therapeutic targets.

**GENETIC VARIABILITY**

Determining what puts some but not others at risk of developing a chronic pain disorder is a crucial step. Nackley’s research has made great strides in this direction with investigations into catechol-0-methyltransferase (COMT), an enzyme that metabolizes catecholamines and usually prevents pain. Her studies show that increased levels of catecholamines and corresponding decreased levels of the COMT enzyme are found in a number of patients with functional pain disorders. A coup for translational research, these findings suggest that genetic predictors could be invaluable tools for deciding on the appropriate therapy.

G-protein coupled receptors (GPCRs) may represent the most promising target in the development of improved pharmacological pain management. They are the largest and most diverse group of membrane receptors in humans, around 70 per cent of which are known to modulate pain. “Some of these GPCRs interact with ‘pro-pain’ molecules to drive pain while others interact with ‘anti-pain’ molecules to dampen it,” explains Nackley. In fact, numerous analgesics work by binding to GPCRs. However, it appears that the variance between patient responses to treatments partly reflects the individual variability of a process known as alternative splicing.

Alternative splicing increases protein diversity, but genetic variations in this process can lead to pathological states. Take mu-opioid receptor 1 (MOR-1), the GPCR responsible for analgesic responses to endorphins and morphine. Nackley recently uncovered evidence of a contrasting role for the splice variant MOR-1K. Instead of delivering analgesic benefit, increased expression of MOR-1K in the central nervous tissue of mice was found to contribute to opioid-induced hyperalgesia (OIH), demonstrating the significance of genetic variability in the mediation of pain. In other words, alternative splicing changed the direction of the pain-relevant GPCR pharmacodynamics.

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**PROFILEING PAIN**

Recently, work at the Nackley Lab has been exploring the potential that microRNAs may hold for drug discovery. Emerging evidence suggests they play an important role in the control of molecular pathways associated with pain, mood and inflammation, but while it is known that microRNAs regulate the expression of pain-relevant genes, their role in chronic pain is poorly understood.

To investigate this role, Nackley has been looking into the relationships between pain, psychological characteristics, cytokines and microRNAs in healthy individuals, patients with chronic pelvic pain (VBD) and patients with irritable bowel syndrome (IBS). Differences between self-reported levels of pain and psychological profiles along with levels of pro- and anti-inflammatory cytokines and microRNAs suggest a potential method for differentiating patient subtypes.

Patients with localised pain may, for example, require a different treatment from patients suffering widespread pain.

Nackley’s research demonstrates the significance of genetic variability in mediating chronic pain, and provides evidence of the utility of genetic predictors in achieving more accurate sub-diagnoses. Nackley is hoping to identify biological mediators that contribute to chronic pain by studying the little known relationship between genotype and biological activity, and its relevance to clinical phenotype. By revealing the pathophysiological mechanisms behind chronic pain, this line of research may help provide the accurate levels of sub-diagnosis necessary to move towards individualised treatments and improvements in the pharmacological management of chronic pain.

Perhaps pain will not need to be managed in the future. It might be a long-term goal of Nackley’s to reduce its prevalence, but her work in risk identification may eventually prevent chronic pain before it occurs.