PAIN CENTRE IMPACT REPORT

PAIN CENTRE VERSUS ARTHRITIS

DEMYSTIFYING PAIN

Musculoskeletal pain can prevent people from living a full life and leave them feeling ‘hidden’ from the world. Finding better solutions to detect, treat, and manage pain is therefore extremely important and this can only be achieved through research. Understanding what pain is, what drives it, and why, needs to be pieced together to tackle pain.

ENTER THE PAIN CENTRE VERSUS ARTHRITIS

In 2010, the Pain Centre Versus Arthritis was established at the University of Nottingham. At the time, the many different things that make each person’s experience of pain unique, and its mechanisms, were not fully understood. Pain Centre researchers have since increased understanding of what causes joint pain, why everybody’s pain is different, and discovered opportunities to better treat pain.

Under leadership of Professors David Walsh and Victoria Chapman, the Centre has received over £5.3 million of infrastructure funding from Versus Arthritis. This has supported network creation, capacity building, tackling unanswered scientific questions, obtaining additional funding, and integrating patient and public involvement.

With this support, the Centre has grown from being a local group of researchers pursuing a wide range of different but complementary research approaches, to its current status as an internationally recognised Centre driving a long-term agenda. This has propelled the Centre to conduct highly influential musculoskeletal pain research, building a legacy that will continue to reduce the impact of arthritis pain on people’s lives.

PAIN CENTRE VERSUS ARTHRITIS

University of Nottingham
UK | CHINA | MALAYSIA

PROFESSOR DAVID WALSH

Co-Director

PROFESSOR VICTORIA CHAPMAN

Co-Director

We are privileged to lead Pain Centre Versus Arthritis together. It is a delight to work with our diverse Centre membership, people with lived experience of pain, with Versus Arthritis and others who share our passion for solving the many problems of chronic pain. The Pain Centre has driven major advances since its inception in 2010.

- We now have a considerable understanding of how the joint, nervous system, mood and thoughts, and people closest to us all shape arthritis pain.
- We have discovered how pain comes about, but also how our bodies prevent or relieve it. We've focused down from big ideas to specific chemicals, cells and brain circuitry.
- We have taken new treatments from animals into people, and taken these insights back into the lab, to create new understanding and treatments.
- We have dug deep into the individual's pain experiences, revealing how each person with arthritis is unique. We have analysed data from thousands of people to discover what is all too frequently shared.
- We have built a platform through which clinicians, neuroscientists, psychologists, biochemists and others can share knowledge.
- We have broken down barriers between researchers and people with lived experience of pain, helping them to make sense of pain, and ensuring we focus on what is really important.
- We have trained a new generation of leaders in pain research, and inspired others around the world to take up the baton.

Our journey has been challenging, full of surprises, excitement and some disappointments. But the journey is not yet over. Too many still suffer from pain. Together, we will provide solutions to relieve the current epidemic of pain.

OUR PAIN CENTRE TACKLES THE FOLLOWING SCIENTIFIC QUESTIONS:

1. How do pain experiences match and differ from one person to another?

Pain is an 'invisible' condition and as a result it can be overlooked, dismissed, and not taken seriously. Large-scale and long-term data sources such as cohorts and repositories, supported by the Centre, put a spotlight on the scale of pain across the UK. These data sources give a platform to the voices of people living with pain, allowing other researchers to gather insights and take inspiration from them, so that their experiences and needs can't be ignored.

2. What drives pain?

Knowing why some people with arthritis get pain and what factors cause pain to improve or worsen is a crucial first step to being able to diagnose, treat, and prevent it more effectively. To this end, the Centre is investigating the different types of pain that exist, the pathways that drive each type, and how these factors work together in combination to create a person's unique pain experience.

3. How can we treat pain in a better way?

Living with pain can take a heavy toll on a person's quality of life. It can affect how we move, think, sleep and feel, along with our ability to work and spend time with loved ones. Alleviating pain is therefore vital. However, pain is a unique experience and so an individual, targeted treatment approach is necessary to select the specific treatments that are most likely to be effective. Centre research has investigated what works best for who, and has supported the discovery and validation of new pharmacological and non-pharmacological pain treatments.

4. How can we build a stronger future for pain research?

Research that reduces and minimises pain needs to remain a high priority in the future. The research questions being tackled must be the ones that have the biggest potential to make a positive impact for people living with pain. To address this, the Centre has provided an environment for patients and the public to be involved in their research, fostered the development of skills in early-stage researchers, built networks of researchers so that pain can be addressed together at a greater scale and pace, and inspired pain researchers across the world to follow in their footsteps by creating their own pain research centre.

£5.3 MILLION VERSUS ARTHRITIS FUNDING HAS LED TO

OVER 450
publications cited more than 20,000 times

OVER £25 MILLION
leveraged funding

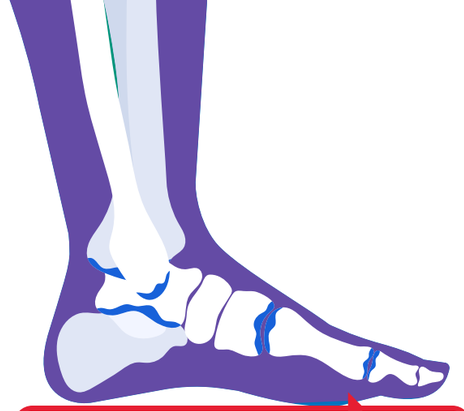
OVER 250
staff and students

OUR RESEARCH IMPACT AREAS

- New Knowledge
- Influence on Policy & Practice
- New IP, Products & Services
- New Networks
- Increased Capacity to Conduct Research
- Leveraged Funding
- Patient and Public Involvement

RESEARCH ACHIEVEMENTS

At the Pain Centre



1999

The Sherwood Forest Hospitals NHS Foundation Trust / University of Nottingham Human Joint Tissue Repository begins collecting human tissue samples, which now includes samples from nearly 4,000 people.

2010

The Pain Centre Versus Arthritis is established with funding from Versus Arthritis.

2010

Growth factors, such as Nerve Growth Factor (NGF), are identified as key contributors to osteoarthritis pain.

2011

Genetic variants in the receptor of capsaicin, which is the main active component of chilli peppers, are shown to be associated with increased risk of painful knee osteoarthritis.

2013

Centre members become part of a European task force which informs non-pharmacological core management of knee and hip osteoarthritis.

2014

The Knee Pain and related health in the Community (KPIC) cohort is initiated, which captures the pain experiences of over 9,500 people.

2015

The Centre for Doctoral Training in Musculoskeletal Health and Pain in Ageing and Wellbeing (CDT MHPAW) is launched.

2016

Interaction with the body's natural cannabinoid system is identified as a potential target for osteoarthritis pain therapies.

2016

Inflammation is shown to contribute to painful changes in spinal cord responses before joint disease manifests.

2017

Centre Co-Director, Professor David Walsh, contributes to the National Pathway of Care for Low Back and Radicular Pain, a national healthcare guideline provider (NICE) endorsed resource for people with acute low back pain.

2017

Pain Centre member Dorothy Auer appointed as Director of Precision Imaging Beacon of Excellence at the University of Nottingham.

2017

Quantitative Sensory Testing research conducted by the Centre is referenced in the American Physical Therapy Association's clinical practice guideline for hip pain, mobility defects and osteoarthritis.

2018

The Investigating Musculoskeletal Health and Wellbeing cohort is initiated, which now includes 8,800 people

2018

A two-way relationship is demonstrated between disturbed sleep and chronic joint pain.

2019

High anxiety is shown to predict an increased risk of knee pain worsening.

2019

Centre members co-develop the Pain research roadmap in collaboration with Versus Arthritis

2019

The UK's largest single investment into pain research, the Advanced Pain Discovery Platform (APDP), is launched and led by Centre Co-Director Professor David Walsh.

2020

Centre members supported a Food and Drug administration submission towards the licensing of a novel treatment for osteoarthritis pain.

2021

The Pain Centre Versus Arthritis releases its Patient and Public Involvement and Engagement strategy.

2021

Interviews with people with knee pain lead researchers to create a simple questionnaire called CAP to measure how the spinal cord and brain influence knee pain

2021

Centre Co-Director, Professor David Walsh, contributes to a workshop that informs the Academy of Medical Sciences to release a report on chronic pain.

2022

Quantitative Sensory Testing research conducted by the Centre provides evidence for a new, potential patented osteoarthritis treatment.

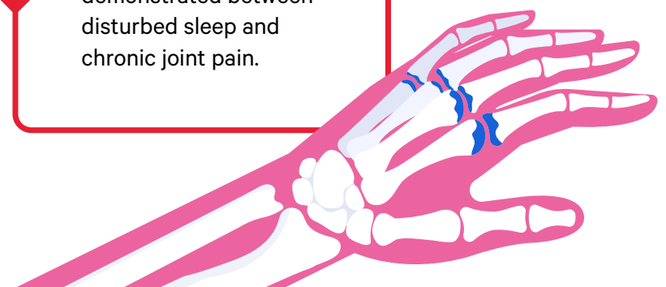
2022

Centre members author the "Cervical and lumbar spine" chapter in the 5th Edition of the Oxford Textbook of Rheumatology, the leading resource for medical professionals in the field.

2023

A two-way relationship is demonstrated between frailty and chronic joint pain.

THE FUTURE



LISTENING TO PEOPLE IN PAIN TO BETTER UNDERSTAND THEIR EXPERIENCES

Why is this important to people with arthritis?

Pain has been called an invisible condition because it is not 'seen' by others, which can leave the person affected feeling isolated and unheard. The voices and experiences of people with pain are being gathered by the Centre, through interviews and discussions, and at scale through large and longitudinal data sources known as cohorts and repositories. These data sources are valuable for different types of research globally, which enables more musculoskeletal research to take place.

The Centre has supported three cohorts and one biorepository:

- Investigating Musculoskeletal Health and Wellbeing (IMHW, 2018)
- Knee Pain in Community (KPIC, 2014)
- Early Rheumatoid Arthritis Network (ERAN, 2002)
- Human Joint Tissue Repository (1999)

Collectively, these four data sources have increased our understanding of musculoskeletal pain and has been used by researchers across the world.

The KPIC cohort was established with financial support from Versus Arthritis. It is particularly valuable because it is representative of a general population rather than focussing on specific groups of people, which could exclude under-represented voices. Adults aged 40 or older from the East Midlands were invited to join the cohort, regardless of whether they had existing knee pain.

Across the three cohorts alone, pain experience data have been gathered from over 20,000 people with, or at risk of, musculoskeletal pain, osteoarthritis or rheumatoid arthritis. Their voices have contributed to many new knowledge discoveries.

- Knee pain can feel like the pain caused by nerve damage, called neuropathic pain, Neuropathic-like pain affects 14% of people in the community. It is more prevalent in women and most tend to experience neuropathic knee pain between the ages of 60-64 years, 10 years later than the age range peak for males (50-54 years).
- Fatigue persists for people with rheumatoid arthritis even after their inflammation improves. Complex therapies might therefore be required to better manage fatigue.
- i-BEAT OA, an internet-delivered, exercise programme aimed as a first-line knee osteoarthritis treatment is superior to routine self-management.
- A nurse-led package of care for knee osteoarthritis pain, including education, exercise and weight-loss advice (where appropriate), was shown to be feasible and could increase uptake of national healthcare guideline (NICE) core recommendations.

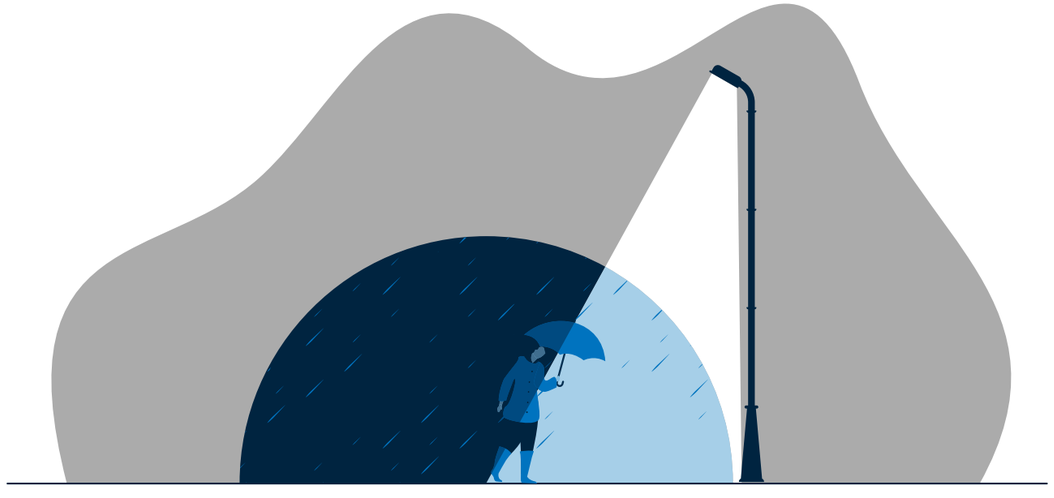
£395,000 was awarded by Versus Arthritis to fund Centre Co-Director, Professor Victoria Chapman, to investigate whether a natural anti-inflammatory molecule called 17-HDHA could be a biomarker of osteoarthritis pain. This project is using samples collected from the Knee Pain in the Community cohort.

The Human Joint Repository has attracted funding from multiple commercial, charitable and Government sources, with substantial contributions from Versus Arthritis. The Repository has received human tissue samples (arthroplasty or post-mortem) from almost 4,000 people with arthritis, as well as people without arthritis. This biorepository uniquely captures pain phenotyping data and demonstrated that:

The growth of sensory nerves between bone and cartilage in a person's knee may contribute to knee osteoarthritis pain. Developing a therapy that reduces this growth may reduce some people's pain.

Knee osteoarthritis tissue, when observed under a microscope, can be placed into broad osteoarthritis subgroups depending on the presence or absence of inflammation. Knowing that osteoarthritis, as a disease, presents itself in different ways emphasises why a more personalised approach to treating pain, rather than one-size-fits-all, is needed.

Several Centre publications have been cited within patents marking novel inventions that can be commercialized. For example, one Centre-authored publication underpinned a 2017 United States patent for a new potential osteoarthritis treatment. Another publication is cited in a 2021 patent for a new potential pain treatment.



34% **of the English population have chronic pain**

WHO IS PROFESSOR ROSE MACIEWICZ?

Who is Professor Rose Maciewicz and how is she linked to the Pain Centre?

I have had an interest in understanding diseases involved with bone and joint tissue remodelling such as arthritis and osteoporosis since 1982. Early in 1991, I decided that drug hunting was for me so the following year, I joined the company now known as AstraZeneca. There, I began and led an osteoarthritis research programme to collect and then analyse samples from people with osteoarthritis as well as people who didn't have osteoarthritis (to act as controls). This collection was the forerunner to the Human Joint Repository now based at Nottingham.

Why was the Human Joint Repository needed?

Drug development is a long process. Animal models are great for many things and can be useful for identifying ideas for drug targets. However, at the end of the day, they are a model. What they show you is how that animal, with an engineered simulation of a disease, is affected by a particular compound. They don't answer all the questions needed to successfully get a therapy over all the hurdles, and into a doctor's hands, as a drug to treat their patients. More appropriate models and a considerable amount of data are needed to prove results in humans with confidence. This is where the Human Joint Repository helps because it enables robust human tissue testing. This allows researchers to see how well a potential therapy works to modify the disease process, potentially alleviating pain for certain patients. Also, it importantly checks whether the compound makes the effectiveness of other drugs, that a person may be taking to treat their co-morbidities, less effective.

Why is the Human Joint Biorepository so important?

The Human Joint Repository continues to collect well-characterised samples of very specialist cell types that are important in pain and osteoarthritis research. They're 'squaring the circle' by bringing lots of different components together that other biorepositories currently aren't. For example, the UK Biobank is the world's largest biobank and very comprehensive in many ways, but it doesn't collect dorsal root ganglia or spinal cord samples which we do at the Human Joint Biorepository. Considering this, Nottingham's biorepository could very well be the largest human joint biorepository providing specialist pain research insights across Europe.

What have been the major successes of the Pain Centre and why?

Back in the early 2000s, researchers would approach pain in a generic way rather than specifically looking at pain within a disease such as osteoarthritis. The Centre has honed the link between pain and osteoarthritis in a more holistic way. They've pushed forward the whole connection between nerve cells, the spine and how that relates to things in your head.

The Pain Centre is doing a good blend of research into how they can help alleviate pain for people both now and in the future. To help patients now, they are developing better ways of assessing pain and investigating psychosocial aspects to improve the effectiveness of medication, such as anxiety and personality traits. In terms of the future, they are actively looking for new drug targets, training the next generation of pain researchers, and building collaborations. They stand on the shoulders of giants so that old ideas can be refined and built upon.

DRIVERS OF PAIN

Why is this important to people with arthritis?

Centre research has greatly increased our understanding of what causes pain to persist, and the various, different ways pain presents itself. These insights are key to preventing pain arising in the first place or preventing the pain from becoming worse.

Pain is a melting pot of different factors.

There are three main pain types, each driven by different but overlapping mechanisms:

- **Nociceptive,** which is triggered by physical threats such as heat, is driven by tissue damage and causes pain in the affected area.
- **Neuropathic**, which is caused by nerve damage and causes symptoms to occur in a wider region – often with `strange' feelings like pin and needles.
- **Nociplastic,** which isn't triggered by any visible threat, is driven by pain sensations being processed by our central nervous system (spinal cord and brain) in an altered way.

Chronic pain affects over

15 MILLION

people in England.

The causes of chronic pain are not fully understood. It is a very complex experience made up of:

- Disease in the joint, known as **peripheral factors**
- The different ways that the body's central nervous system (spinal cord and brain) processes pain signals, called **central factors.**

Pain Centre researchers are world-leaders in understanding the balance between peripheral and central factors contributing towards pain. This research could enable pain to be measured in a more comprehensive way, so that treatment can become personalised to a person's unique pain sensation:

- When knee pain first starts, it is mainly driven by disease or injury in the joint (peripheral factors). Central factors such as anxiety, on the other hand, are often the main drivers for knee pain worsening.
- Neuropathic-like knee pain is driven by central factors. It feels as though nerves are damaged, although often they are not.
- Knee pain that has gone on for a long time is usually driven both by peripheral and central factors, in varying proportions. Understanding this balance helps decide what treatments are most likely to be helpful for any one person.
- Centre researchers, in collaboration with academics from Aalborg, Denmark, identified a brain signature underpinning central factors driving pain. This signature is associated with greater blood flow changes in two brain networks known as the salience and anterior network hubs. These network hubs are important for processing external (environmental) and internal (emotional) events, and 'weighing up' which is the most important to guide our behaviour.

EVERYONE'S PAIN JOURNEY IS DIFFERENT

The Pain Centre has shown that, for different people, pain may get better or worse. Centre research on pain progression has led to many important discoveries:

Predicting chronic pain

- Various factors can worsen pain progression for an individual, even when their joint disease has settled. These factors include smoking, living with high levels of disability, collectivism, and agreeable personality traits.
- Persistent, severe fatigue is experienced by over half the rheumatoid arthritis population. We may be able to predict from patient characteristics at the point of diagnosis who will be most affected by fatigue. This could tell us who would most benefit from targeted, preventative treatment to stop fatigue in its tracks. Women with worse mental health, pain and functional ability at presentation of rheumatoid arthritis are more likely to experience fatigue.

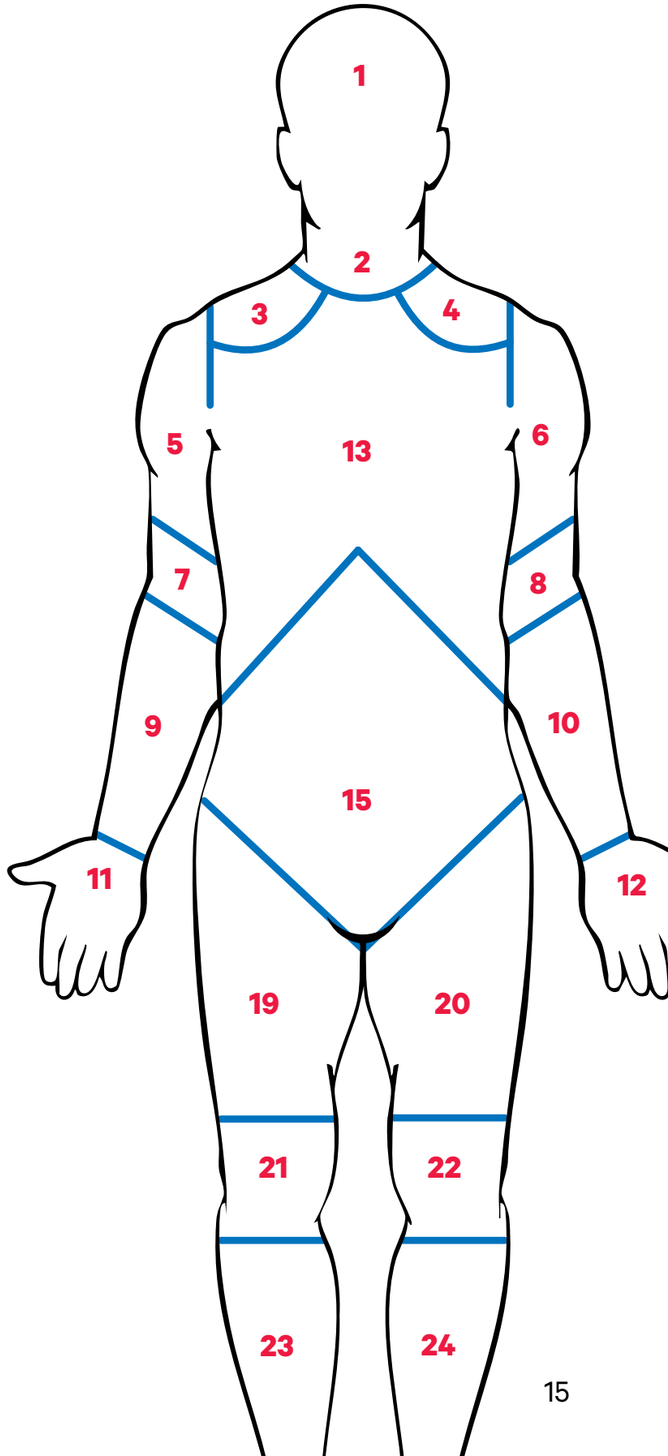
The wider impacts of chronic pain

- Chronic pain affects not only wellbeing and physical ability, but social and civic engagement such as voting. Understanding the social impact of pain is essential to prevent those affected by arthritis being a forgotten and unrepresented section of the community.
- The Centre conducted a key study that examined the interplay between arthritis pain and functional disability. It showed that, despite pain being the most common reason why people limit daily functioning, even when pain improves, daily function doesn't always improve.

A SIMPLER TOOL TO ASSESS CENTRAL NERVOUS SYSTEM ASPECTS OF PAIN

Two tools currently used to assess how the brain and spinal cord affect arthritis pain are called quantitative sensory tests (QST) and functional magnetic resonance imaging (fMRI). QST measures the sensation and pain thresholds for pressure, touch, temperature, or vibration. fMRI evaluates blood flow in the brain to show which parts are activated when pain is being processed. Both tools can take an hour, plus preparation and require specialist equipment.

Patient and Public Involvement impact: The Centre co-developed and validated an alternative tool, known as the CAP questionnaire, to measure Central Aspects of Pain. CAP was co-developed using interviews from people with knee pain, and supported by the Centre's Patient and Public Involvement group. The CAP questionnaire brings together diverse aspects of the pain experience, such as anxiety, depression, catastrophizing, fatigue, sleep disturbance, and difficulty thinking straight. CAP is a simpler method to assess an individual's pain experience than QST or fMRI, and has many other advantages. It opens the way for more routine assessment in the NHS of important contributions from brain and spinal cord to arthritis pain.



WHO IS DR KEHINDE AKIN-AKINYOSOYE?

Who is Dr Kehinde Akin-Akinyosoye?

My PhD was funded by Versus Arthritis through the Pain Centre. I am now a Lecturer in Population Health at Hull York Medical School.

What research did Kehinde do whilst at the Pain Centre?

I led a research study to develop CAP-Knee, a knee-pain clinical assessment tool that was co-designed by people with arthritis. The Pain Centre's dedicated Patient and Public Involvement Manager coordinated opportunities for people with arthritis to give feedback on whether it was acceptable. Nurses from Sherwood Forest Hospital also gave feedback so that the questionnaire would be acceptable and useful to not only the person asking the questions, but also the person answering them.

Since leaving the Centre, opportunities have arisen to modify the questionnaire for assessing pain in other conditions, such as rheumatoid arthritis.

How has the Pain Centre helped train and develop Kehinde for her future?

It wasn't just a case of completing my PhD and moving on. At the Centre, I learnt many core research skills, like communication and statistics, that I still use. This set me on the right path for my current position as a lecturer.

The data from the Centre's cohorts are a great training resource for PhD students to develop their statistics skills. The cohorts contain such a large scale of data that there was always some statistics work and skills to be developed with it.

The communication skills that I developed through the Centre helped me secure my job now as a lecturer. I use the opportunities that I now have to spread information that will help better prepare medical students for what they will see in practice. That includes exposing them to potential clinical assessment tools such as CAP.

What are the strengths of the Pain Centre?

The collaborative and networking spirit, it's really driven into the framework of the Pain Centre. I may have left the Centre, but I am still in contact with many of its members. This has fed into how I practice research now.

Another strength would be its culture, the people there are really friendly. Being there was a very enriching experience for me as a student. The researchers practice what they preach, Professor Weiya Zhang leading us through a Tai Chi session every Friday is just one example of this. I had some of the best years of my life in Nottingham. My first child was born in the middle of my PhD and they gave me so much support for this.

WHO IS STEVIE VANHEGAN?

Who is Stevie Vanhegan?

I have been involved with Pain Centre research since its inception in 2010. It all started for me by first attending a patient and public involvement training event at Nottingham. Since then, I have worked in various research projects at the Centre. Back then, I suspected that I had knee osteoarthritis. It was subsequently diagnosed and resulted in two knee replacement surgeries. I have now been told that I also have osteoarthritis in my neck and hands. I also live with asthma and inflammatory bowel disease.

How does Stevie get involved with research at the Pain Centre?

Before a project starts, I review grant applications. I also look at study materials such as patient information sheets and recruitment packs once the study has begun. In one current study, I was involved with going through the testing procedure before the actual participants took part. With my feedback, they optimised the procedure so that it will be more comfortable and shorter for those taking part.

Why is patient and public involvement important and a success at the Pain Centre?

I feel very strongly that nothing should be designed, whether it's a building or a system or a research study, without 360-degree stakeholder input. Otherwise, it's just not going to be as good as it possibly could be.

Patient and public involvement is a success at the Pain Centre because of the people there. I've made some really good friends through the Centre and David Walsh, in particular, is a really good man to work with. He's very enthusiastic, someone I can trust, and he's someone that really puts PPI on the platform where it should be.

The feedback I get from researchers is that I make them think about aspects they've never considered before; and this approach is used beyond the Centre in other institutions. Recently, a researcher asked for input into their European-funded big data project on osteoarthritis and co-morbidities. I noted that the research design didn't take into account the very important factor of menopause. This has now been included, meaning the research will be far more relevant for women.

How has being involved with research at the Pain Centre helped Stevie?

Through the Pain Centre, I am now involved with a research project called the Advanced Pain Discovery Platform (APDP). From this, my understanding of pain in general has improved which has helped not only me, but my husband who lives with trigeminal neuralgia, and my friends whom I offer guidance and support to.

TARGETTING THE ROOT CAUSE OF PAIN

Why is this important to people with arthritis?

Alleviating pain is crucial so that people with arthritis can live as full a life as possible. The Centre has discovered and validated potential treatments for reducing pain by identifying 'windows of opportunity' to stop drivers of pain in its tracks.

Discovering new targets

The Centre has discovered several targets to attack the root cause of pain:

- VEGFR2, a molecule that is important for helping new blood vessels to grow, promotes the spread of pain in inflammatory arthritis. Therapies that block VEGFR2 could reduce pain.

- A phase 3 clinical study of an anti-NGF (Nerve Growth Factor) drug called tanezumab showed that it improved pain symptoms more than non-steroidal anti-inflammatory drugs, but also caused rare but serious joint damage.

  This clinical study stemmed from Centre research that identified NGF expression as having an important link to arthritis pain .The clinical study findings highlight the complexity of developing treatments to reduce pain in osteoarthritis and the difficult balancing act between benefits and risks. Tanezumab is now no longer being developed as a potential drug, but important lessons have been learned about how pain and joint structure are reciprocally linked. Drug testing in the future will take account of how pain-relieving treatments might affect joint structure, as well as how treatments that might preserve joint structure can affect pain.

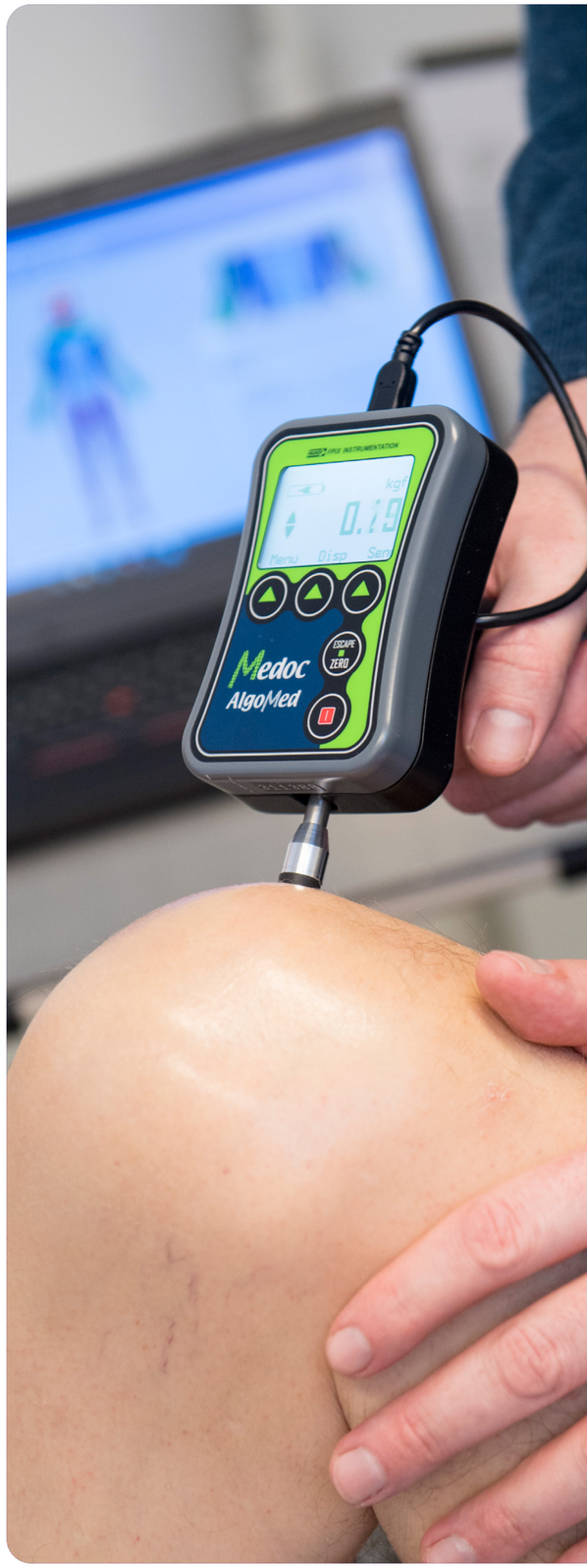
- TRAP5b, a marker molecule associated with bone tissue breakdown, is associated with high severity pain. Knowing this could help predict people who will benefit particularly well from treatments that target bones to relieve pain.

A NEW WAY OF THINKING

Centre researchers have applied an experimental approach known as **back-translation** to identify potential targets to slow down or prevent pain. The usual drug discovery process taken by researchers goes from the lab to research studies in humans, to the patient's bedside, but this is often slow or fails. Back-translation reverses this thinking - findings from human clinical studies are used to inspire a new hypothesis to test in the lab. One successful example of back-translation is:

The sEH (soluble epoxide hydrolase) gene was shown to play an important role in osteoarthritis pain in a cohort of people. Before this study, sEH was known to be correlated with inflammation, in general, but its potential link with osteoarthritis pain was not fully understood. Centre lab studies demonstrated that sEH is a target for treating osteoarthritis pain.

After the sEH target was identified to treat osteoarthritis pain, Professor Vicky Chapman worked with a US pharmacological company called EicOsis to raise over $1.5 million capital investment. A drug candidate for an sEH inhibitor is now undergoing human clinical trials.



WHAT WORKS BEST FOR WHOM?

Pain is personal and multifaceted, and so should be treated accordingly in a targeted way. Better treatments can be provided if they are tailored to pain characteristics presented by the patient, rather than diagnosis alone.

Capsaicin

The Centre has applied a patient-oriented approach using an experimental process known as the n-of-1 methodology. When a treatment has been shown to work well for a large population, it can lead to it being recommended in a one-size-fits-all way. Centre researchers have challenged this by using the n-of-1 methodology, which focusses on individual response rather than group average. Without applying this methodology, they would not have been able to show that:

Capsaicin cream works very well for some but not all people for treating osteoarthritis pain. This conflicted earlier reports which suggested that capsaicin worked a little bit for everyone.

Opioids

Opioid painkillers, e.g. codeine, can be prescribed to offer relief from moderate to severe pain when other treatments haven't worked. However, because of risk of side effects, such as addiction and overdose, healthcare professionals are advised to strictly monitor prescriptions and avoid prescribing opioids wherever possible.

People with anxiety are less likely to get pain relief with opioids, and that anxiety is a barrier to full analgesic benefit from opioids in a rat model of osteoarthritis. This is an important factor that should be considered by healthcare professionals to ensure that people in pain, with high anxiety, aren't being over-prescribed, and that anxiety itself is treated appropriately.

Joint replacement surgery

Not everyone with arthritis will need joint replacement surgery, but it can help some to reduce pain and improve mobility. Surgery works, but up to one fifth of people experience persistent pain in the long term after total knee replacement. Being able to predict who will and won't benefit from surgery would be incredibly valuable.

Pain characteristics presented before surgery can predict pain after total knee replacement surgery. Individuals with neuropathic-like symptoms, such as electric shock sensations and burning pain, are most at risk of experiencing persistent pain following surgery.

WHO IS DR CINDY MCREYNOLDS?

Who is Dr Cindy McReynolds?

I am CEO of a US biotechnology based in California called EicOsis. EicOsis is committed to developing a new class of safe, non-addictive and effective oral treatments to alleviate pain and inflammation. I have been CEO of EicOsis since early 2023 and during that time have worked closely with Pain Centre Co-Director, Professor Vicky Chapman.

What is soluble epoxide hydrolase?

Soluble epoxide hydrolase (sEH) is an enzyme involved with inflammation. Dr Bruce Hammock, CSO of EicOsis, co-discovered the enzyme in insects over 50 years ago. Since then, more research studies have taken place in different animals which has demonstrated its association with inflammation and its potential to treat neuropathic and inflammatory pain.

Before Pain Centre research, sEH was known to be associated with inflammation for several conditions but what it actually did and why was not fully understood. Vicky Chapman's research helped change that.

How and why did Pain Centre research become influential in EicOsis' work?

Vicky Chapman identified increased sEH activity in arthritic joints. Dr Bruce Hammock is a leader in this field, so Vicky reached out to see what he thought about her findings. Vicky's research caught our eye because not only did her results from humans align with Bruce's previous findings in animals with other diseases, but her findings were especially robust. This showed that sEH really had an impact on disease modification and it wasn't just a correlative effect.

Ultimately, Vicky's work provided the justification for us to investigate developing an sEH inhibitor to specifically treat osteoarthritis pain in humans.

What is EicOsis working on now and next?

EicOsis has completed its first human clinical study to demonstrate the safety of sEH in humans. There were no clinically significant adverse events, so that means we are ready to move into efficacy testing and have secured grants to do exactly this. We have also been awarded another grant to see whether sEH could be effective in specifically treating neuropathic pain in veterans with spinal cord injury.

Next, we are actively fundraising for a $40M financing round as well as grants to evaluate osteoarthritis pain in patients with kidney disease. Vicky's research is a key part of the scientific background that we present to potential investors to emphasise the significance of this target.

Why is this work so important?

sEH activity is associated with several inflammatory diseases such as osteoarthritis, cardiovascular disease, Alzheimer's and Parkinson's. This means that an sEH inhibitor drug could have the potential to be effective and safe in treating a number of different diseases.

Also, it's important to investigate at a molecular level why some people really are in more pain than others. If EicOsis can help people affected most by pain, and supplement them with safe drugs to help their disease, then we can improve their lives.

A NEW WAY OF WORKING TO BUILD A LEGACY

Why is this important to people with arthritis?

To discover and implement life-changing research breakthroughs, it takes consistent financial backing, expertise, research support, connections, influence and many other things. The Pain Centre Versus Arthritis has fostered a platform for all these things to thrive, building the foundations for continuing and future research into arthritis pain. By people working together to build new partnerships, greater and more impactful discoveries can be made than by any single researcher, discipline or institution.

BUILDING NETWORKS

The Centre has been successful in forging multi-disciplinary and multi-sector collaborations. They have connected researchers across fields so that pain research breakthroughs can be discovered at a greater scale, most evidently through three consortia:

1. Advanced Pain Discovery Platform – the Pain Centre is both a recipient and collaborator of the UK's largest single investment in pain research ever, funded by UK Research and Innovation, Versus Arthritis, Eli Lilly and Medical Research Foundation. Pain Centre Co-Director, Professor David Walsh, is Director of the APDP.

2. Biomedical Research Centre – in 2015 Nottingham was selected to host the first NIHR Centre to focus on musculoskeletal research, in addition to four other themes.

3. Precision Imaging – one of the six Beacons of Excellence at Nottingham University, the Precision Imaging Beacon builds on Nottingham's reputation as the birthplace of Magnetic Resonance Imaging (MRI) to conduct transdisciplinary world-leading research. It is now developing innovative imaging tools for major causes of disability, including musculoskeletal conditions.

Across these three consortia, over £8.5 million has been generated to fund more musculoskeletal research. In addition to this, Nottingham University's largest ever funding award, totalling £29.1 million, was granted to purchase the UK's most powerful MRI scanner. Pain Centre Versus Arthritis is building upon its expertise in brain imaging to unravel pain mechanisms and inform new treatments that might prevent or reverse changes in the brain that make chronic pain such a devastating experience.

The Precision Imaging Beacon is one of six beacons established at Nottingham which have together generated 500 jobs, offered 40 PhDs and opened an office space for over 40 researchers.

APDP ADVANCED PAIN DISCOVERY PLATFORM

NIHR | Nottingham Biomedical Research Centre

TRAINING FUTURE PAIN RESEARCH LEADERS

The Centre for Doctoral Training in Musculoskeletal Health and Pain in Ageing and Wellbeing was launched in 2015. Providing PhD training for clinical and non-clinical scientists, the programme has been led by the Pain Centre and delivered collaboratively by three research Centres of Excellence funded by Versus Arthritis: the Pain Centre, Medical Research Council Versus Arthritis Centre for Musculoskeletal Ageing Research (CMAR), and the Sports, Exercise and Osteoarthritis Centre.

Centre funding, and complementary consortia, enabled a Patient and Public Involvement and Engagement (PPIE) group to be established and a dedicated PPIE manager to be appointed. The Centre's PPIE group has doubled in size since its inception. One PPIE activity is focussed on delivering training on the nature and value of PPIE to undergraduate medical students and postgraduate researchers.

OVER 50

PhDs students have been trained at the Centre and a fifth of these have progressed to become Centre staff members.

INSPIRING MORE WORLD-LEADING PAIN RESEARCH

The infrastructure approach of a centre enables the complexities of the fundamental research questions to be considered from different perspectives using a wide range of experimental methods. An individual centre has scientific strength alone, but working with other centres who have their own unique strengths adds more power. The Pain Centre has formed mutually beneficial connections with other centres based in Denmark and the US. The Pain Centre at Nottingham inspired the creation of that in Chicago.

The Pain Centre has enabled over $15.5 million of dedicated osteoarthritis pain research to be leveraged by the Chicago Center on Musculoskeletal Pain (C-COMP).

A Chicago-based pain lab group of three researchers has grown into a dedicated Centre comprising over 15 researchers and 250 members. A core aspect of this Chicago Centre, similar to the Pain Centre, is focussed on training the next generation of researchers.

WHO IS DR VASILEIOS GEORGOPOULOS?

Who is Dr Vasileios Georgopoulos?

I am a qualified physiotherapist and post-doctoral fellow at the Pain Centre. I moved to the UK, from Greece, back in 2013 for my master's and then completed my PhD through the Centre in 2016. I have stayed here since!

What inspired you to focus on pain research and join the Centre?

The main reason why people see a physiotherapist is for their pain - you're exposed to it every day. During my master's, I learnt the theory behind why pain starts and became fascinated with the science behind it. After my Masters, I did a placement at a local hospital and whilst gaining this hands-on experience quickly realised that what I wanted and needed to know more about was pain research. This led me to apply for a PhD at the Pain Centre.

What pain research has Vasileios completed and what is he working on now?

My PhD focussed on central sensitisation in low back pain. I also did an observational study on people from the local community with chronic back pain to establish better ways to understand their pain experience. As a post-doctoral fellow, I am currently investigating the links between components of synovial fluid in the knees of people with chronic knee pain and exploring the mechanisms of pain in chronic conditions.

In what ways has the Pain Centre helped you further your career?

Centre Co-Director Professor David Walsh was integral to me getting the PhD scholarship in the first place. One requirement of my scholarship was that it had to become my full-time role, which would leave me with no time to work as a physiotherapist. This was a dilemma because continuing to work in the clinic, for me, is very important to make sure that I remain competent. With Professor Walsh's permission, connections, and support, we found a post for me that could work around my studies. I became a chronic pain NHS clinician. This was transformative to me both personally and professionally. It's this intangible type of support that I have really benefitted from.

The Centre supported me with my professional development, which is helping me improve my skills as a physiotherapist. Now, I help supervise students at the School of Medicine to develop their careers and elevate their projects.

What is the best thing about the Pain Centre?

From day one, you are immersed in an environment where pain expertise is second-to-none. Through the Centre, you are part of a big vision, working with a team of people who are investigating pain from many different perspectives. Working with researchers at the frontiers of the field enables you to build off and add to the best, latest research from the get-go.

WHO IS DR SARA GONÇALVES?

Who is Dr Sara Gonçalves?

I moved from Portugal to do my PhD, which I completed in 2021, and continued to do pain research at Professor Vicky Chapman's lab for a post-doc. I was at the Centre for six years. Now, I am working on a neuropathic pain research project at the University Medical Centre Utrecht, in the Netherlands.

What inspired Sara to become a pain researcher at the Centre?

During my biology undergraduate degree, back in Portugal, there was one rotation at a pain laboratory. I was fascinated by what I saw and fell in love with the field, so I decided to focus on chronic pain for my master's. Then, whilst looking for a PhD opportunity, I came across the Pain Centre and made contact. Vicky was very approachable, told me more details about the research project, and invited me to an interview. It sounded exciting, so I moved to a new country and city, where I had never been before, to start working at the Centre.

What pain research did Sara do at the Centre?

As part of my PhD in collaboration with Vicky Chapman and Tobias Bast, I studied in rats whether chronic osteoarthritis pain affected cognition, specifically memory and behavioural flexibility. In this model, we didn't find a direct correlation.

I was also involved in the project studying the effect of anxiety on the effectiveness of opioids alongside Dr Amanda Lillywhite and Dr Steve Woodhams, who led this project. Their transdisciplinary links with brain imaging specialist researchers and psychologists was crucial to run the study and form valid conclusions.

How did the Pain Centre help Sara with her research?

The Centre has a really nice environment and its approach to openly sharing knowledge is one reason for this. Regular Centre-wide meetings took place which facilitate knowledge exchange so that different types of research can be discussed with different stakeholders, such as clinicians, patients, and researchers. These meetings were really useful to spark discussion, hear varied perspectives about a particular topic, and identify where our research crosses over different departments and can benefit other researchers.

It was amazing for me, as a PhD student doing early lab research, to have exposure to people with lived experience at these meetings. They helped me to think big, recognise that my research may not be reaching patients yet but is still important, and be inspired with the idea that maybe one day I could help someone to discover something that will help alleviate their pain.

WHO IS PROFESSOR ANNE-MARIE MALFAIT?

Who is Professor Anne-Marie Malfait?

I am Director of the Chicago Center on Musculoskeletal Pain (C-COMP), which is funded by the National Institute of Arthritis and Musculoskeletal and Skin Diseases. At our Centre, we lead research and training programmes aimed at investigating the mechanisms underlying pain associated with musculoskeletal diseases.

How did Anne-Marie first become involved with Pain Centre researchers?

I used to work for Pfizer in the mid-2000s. At that time, we were doing genetic association studies on very large populations of people with osteoarthritis. After I left Pfizer, I set up my own lab and then met Professor Ana Valdes from the Pain Centre at a research conference.

How has the Pain Centre benefitted Anne-Marie and influenced the wider pain research community?

At the time I set up my laboratory, comprising of myself, a technician and a post-doc, the only serious group in the world that studied pain in osteoarthritis from a basic, mechanistic viewpoint was the Pain Centre in Nottingham. For many years, it was just us three people. Ana Valdes visited us a couple of times and was incredibly helpful. She helped us handle and interpret data that was completely new to us.

During this time, I became hyper aware that there was a lack of concerted research addressing specific mechanisms of pain in rheumatic and musculoskeletal diseases in the US. That's why we applied for a Center grant from the National Institutes of Health (US government funder). Professor David Walsh from the Pain Centre, and an American pain researcher Professor Tony Yaksh, were instrumental in us winning the Centre grant. David Walsh ran through our draft application and, using his experience from the Pain Centre, improved its vision.

Since then, we have recently been successful in winning a consortium grant. This is a direct consequence of research that David Walsh started at the Pain Centre. In summary, this means that our working relationship with the Pain Centre in Nottingham has so far enabled us to leverage over $15.5 million worth of dedicated osteoarthritis pain research in the US.

Why are centres, dedicated to pain research, so important for the future?

Our Center and the Pain Centre don't compete with one another, we complement each other. We are both building a new generation of future pain researchers. Through our Centre, we have so far awarded nine $25,000 pilot grants to kick-start small-scale research projects. We also provide hands-on training and run virtual journal clubs which are attended by researchers from all over the world. This helps early-career researchers in particular, to learn more about the field so that they can conduct pain research earnestly.

WHO IS PROFESSOR THOMAS GRAVEN-NIELSEN?

Who is Professor Thomas Graven-Nielsen?

I am Director of the Center for Neuroplasticity and Pain (CNAP) based at the University of Aalborg in Denmark. The CNAP was established in 2015 and is funded by the Danish National Research Foundation. We do research to understand why some individuals develop persistent pain and others recover following an acute episode of pain.

Why does Thomas collaborate with the Pain Centre and what benefits does this collaboration bring?

Our Centres have different strengths and so working together helps improve our research, it's a win-win relationship. One strength of the Pain Centre is their large and well-established arthritis pain cohorts. In Denmark, we don't currently have something like this and so it is very useful for us to access this ready-made dataset. It would take a lot of time and energy for us to create an asset that matches theirs.

Another strength of the Pain Centre is their expertise and facilities for brain imaging, neuroscience and clinical research. Our Center grant from the Danish National Research Foundation is focussed mostly on investigating fundamental pain mechanisms which means that we typically run our clinical studies outside CNAP. Working with the Pain Centre at Nottingham has given us an additional route to do clinical research in humans.

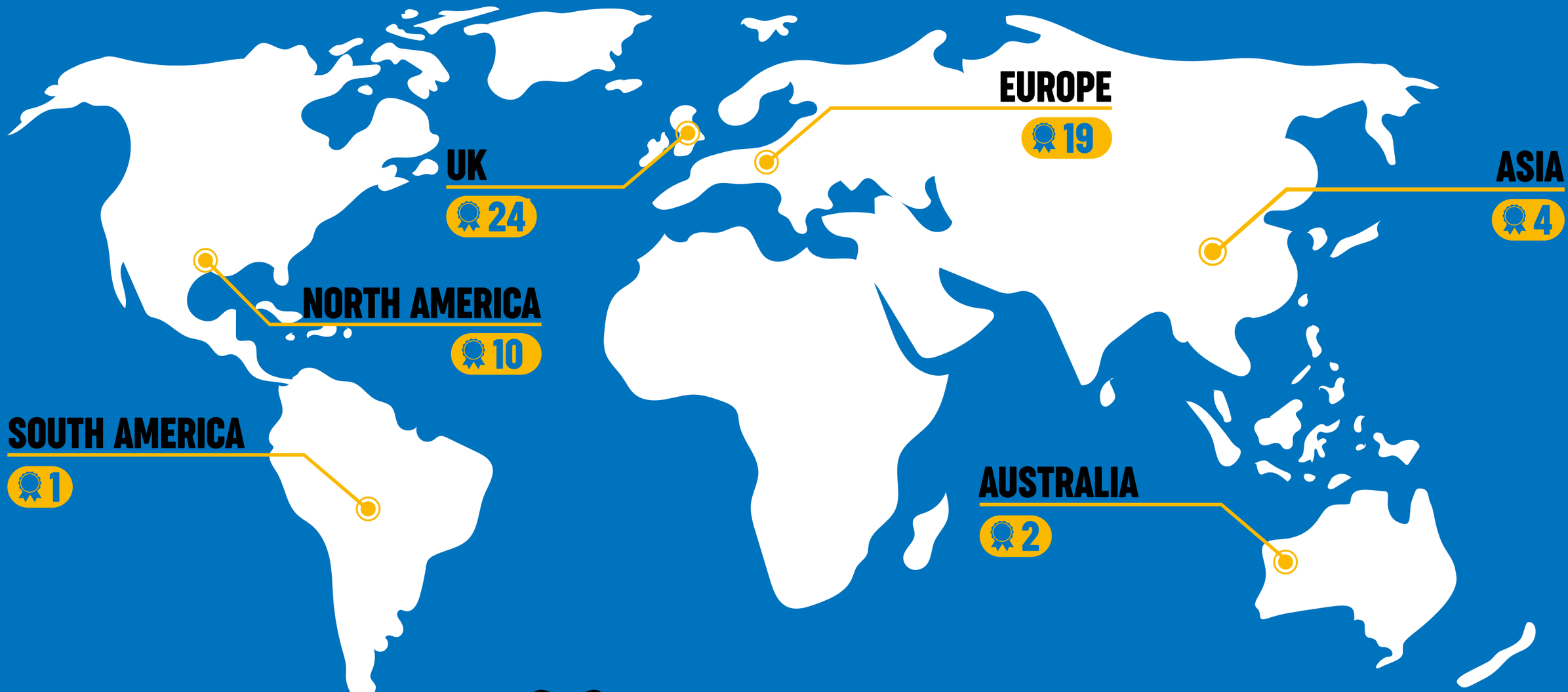
What research has Thomas worked on with the Pain Centre?

One research study that we have worked on together showed there are certain patients with knee osteoarthritis whose pain won't be alleviated through knee replacement surgery. This collaborative study brought our individual strengths together - CNAP are leaders in profiling different types of pain mechanisms, whilst the Pain Centre provided us with access to their existing clinical study participant groups.

We still have a way to go before we can actively predict specifically who should and shouldn't be operated on in the first place, but our understanding of the pain system is far better than it was 10-15 years ago. We can now profile the pain system from a much more pragmatic and holistic perspective.

Why is pain research so important?

Many patients with pain, such as low back pain, recover without needing treatment within a few months. It would be greatly beneficial to patients and our healthcare system if we were able to subgroup patients to predict who will and won't recover. That way, more resource and research activity can be focussed on developing targeted treatments for those who need it the most.



RESEARCH REACH

62 GLOBAL COLLABORATORS

THE CENTRE COLLABORATES ACTIVELY WITH 38 ACADEMIC INSTITUTIONS, 16 CLINICAL SERVICE PROVIDERS AND 8 INDUSTRY PARTNERS, SPANNING 21 COUNTRIES.

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