How did you come to develop an interest in intracerebral haemorrhage (ICH) outcomes?

I trained as a neurologist and became interested in intensive care while completing my residency in neurology at Duke University. I took an anaesthesiology course to equip me to practise intensive care neurology, and while finishing my training I became interested in brain haemorrhage. It was a relatively understudied field at the time; we were beginning to study the disease but lacked knowledge of fundamental pathophysiology, and I felt we could do better. That’s what drove me into the lab.

Why have you focused on the effects of sex and gonadal hormones on ICH outcomes?

It was serendipitous. We were using transgenic mouse models of haemorrhage, and without realising it received two cages comprised solely of female mice. This was a complete mistake, as therapeutics are almost exclusively developed in male preclinical models. We ran them through the experimental protocols and recognised that their recovery times were dramatically faster than those of the other mice – approximately twice as fast. So we asked the question: what was different about these mice? It turned out they were all female. In checking the literature, I realised that there was limited information on sex or gender differences in either preclinical models or human ICH. This discovery has gone on to inspire a host of ideas and projects.

In what way does unveiling the sex differences in ICH response contribute to the wider clinical and research area?

Firstly, if we can demonstrate associations between serum gonadal hormone concentrations and good long-term outcomes, it will pave the way for the use and regulation of these hormones as a therapeutic strategy.

Secondly, the physiology of gonadal hormones is extremely complicated, so any knowledge about what’s going on in a human both during and after injury is useful. It allows us to ask the right questions about the effects of gonadal hormones on the recovery phase following a brain injury.

Thirdly, we can use these data to question how we design clinical trials. If we know that women or men recover differently then that needs to be factored into how we build a clinical trial for therapeutics for ICH.

With your experience in conducting clinical trials, what differences have you observed between multicentre trials and smaller, ‘home grown’ projects?

Larger and smaller studies are both interesting. I like doing both, but they have different uses and the way to approach them is distinct. The input for a large multicentre trial comes from several places, so it’s a bit like a big steam ship: although you can change the course, it’s not easy. On the otherhand, small trials are more like speedboats: if you want to change direction, oftentimes you can do it on a dime. It still takes some effort, but it’s a lot easier than for large trials. The main reason for this comes down to what they’re trying to accomplish. Large trials, in theory, should have their question well refined and their study design well hammered out, while smaller studies are more about figuring out what the right question is and how best to study it.

Do you predict you will have translated your findings into a treatment within the next five to 10 years?

If you’re a betting person, I’m sure you’d bet against me: in terms of therapeutics we don’t have anything that works yet, and there have been more than a few failures. However, in terms of mechanisms – our understanding of what occurs – a lot of things have begun to and continue to translate. I want to be optimistic and say we have a good shot; indeed, we may only be five years away. Despite historical under-funding in this area, the current rate at which scientific data are being generated is astronomical, so maybe it won’t be long before we understand what’s going on in humans after ICH and find a way to effectively modify that.
Tackling intracerebral haemorrhage

At Duke University, USA, scientists are conducting groundbreaking research on the factors that impact recovery following intracerebral haemorrhage, with a view to guiding development of novel, patient-tailored therapies.

**INTRACEREBRAL HAEMORRHAGE (ICH)** is the only stroke subtype for which there remains no effective treatment. It is well-established that a number of factors impact ICH recovery, such as ethnicity and age. Similarly, it is well-known that gonadal hormones (progesterone, oestrogen and testosterone) are neuroprotective. However, there has been relatively little research on the effects of sex differences on ICH outcome and the extent to which gender, age, ethnicity and gonadal hormones interact with each other.

An improved knowledge in this area would guide researchers in the development of novel ICH therapies. In light of the fact that stroke is currently the fifth leading cause of death in the US, and that ICH accounts for 50 per cent of all stroke mortalities, any findings that can be translated into clinical benefits in this area will have significant impact.

**SEX AND THE BRAIN**

At Duke University, clinician-researcher Dr Michael L James – who is best known to his colleagues by his middle name, Luke – leads a research programme aimed at determining the impact of sex and gonadal hormones on ICH outcomes, with a focus on elucidating the interacting effects involved. He has a particular research interest in the mechanisms through which sex and gonadal hormones modulate acute inflammation following ICH and, in so doing, impact recovery.

His early research in this area used a murine model of ICH that he had previously developed to explore the question of how sex and gonadal hormones interact with age.

The lab’s experiments generated a number of interesting findings. For example, older mouse models without gonadal hormones had worse outcomes than those with gonadal hormones, and older mouse models without gonadal hormones that were treated with progesterone had better outcomes than those that were not treated.

More recently, James has been leading work to elucidate the underlying mechanisms involved in these effects, examining progesterone’s impact on microglial cells. “Progesterone downregulates many inflammatory pathways, including secretion of cytokines and chemokines from the microglial cells, and probably influences microglial polarisation,” he explains. “Early data suggest that progesterone may move microglial cell populations towards anti-inflammatory states, rather than proinflammatory ones.”

**RETROSPECTIVE ANALYSES**

The lab has also been using retrospective and prospective datasets to carry out an analysis of sex effects on ICH outcomes in human populations. Initially, the researchers analysed Duke University’s population of ICH patients, which comprises approximately 200 individuals. This study confirmed a strong age-sex interaction, with male outcomes shown to decline linearly with age and female outcomes dropping significantly at around the time when menopause generally occurs. This led the team to hypothesise that individuals with gonadal hormones will have better ICH outcomes, while women without these hormones (ie: post-menopausal women) will have worse ICH outcomes.

Fewer than 25 per cent of patients regain complete independence following intracerebral haemorrhage

Less than two-five per cent of patients regain complete independence following intracerebral haemorrhage.
Unfortunately, the Duke University dataset was insufficient for testing this hypothesis, as it did not include long-term outcomes. For this reason, the researchers turned their attention to larger and more detailed datasets, including both the American Heart Association’s Get With The Guidelines – Stroke and Ethnic/Racial Variations of Intracerebral Haemorrhage (ERICH) databases. While these investigations are ongoing, early evidence points to potentially conflicting sex effects on early mortality and long-term neurobehavioural recovery after ICH; of course, any sex-specific results require the clarification of gonadal hormone effects. These findings highlight the complexity of sex-based research and, specifically, the effects of varying levels of gonadal hormones across the human life span.

DELVING DEEPER
The group’s work does not end there, however. James plans to address a major shortcoming of the researchers’ current dataset work to date: namely, that they have not included exact measurements of serum gonadal hormone concentration. They will therefore perform a fresh statistical analysis of the data and blood samples within the ERICH database.

They have two specific aims. The first is to define the interdependent influences of age, gender and ethnicity on clinical outcomes after ICH in the ERICH patient study population. The second is to identify associations between serum gonadal hormone concentration and gender-specific outcomes after ICH through a tissue sample biorepository and large study population.

These studies will pave the way for future research aimed at evaluating the efficacy of exogenously administering gonadal hormones as a novel therapy for improving ICH recovery in a number of ways. It will define the gender-specific age range at which patients are most at risk of poor ICH outcome, and determine the relevance of gender and presence of gonadal hormones when testing potential therapeutics.

FROM BENCH TO BEDSIDE
James plans to continue building a large human tissue repository that can address questions of acute and sub-acute inflammation. “I want to take what the animal models have taught us and see how well it translates to human disease, particularly the activation of microglial cells and how they polarise,” he explains.

He also has plans to shift his research focus beyond the acute injury phase, to gain a greater insight into the mechanisms and pathophysiology that influence long-term outcome – all of which represent potential therapeutic targets.

Dr Michael L James leads a research programme aimed at determining the impact of sex and gonadal hormones on intracerebral haemorrhage outcomes, with a focus on elucidating the interacting effects involved.

Ultimately, all of the research carried out in the James lab is designed to contribute to the development of novel, patient-tailored therapies for improving ICH recovery in patients of diverse ages, genders and ethnicities – whether by guiding future clinical trials to account for sex differences, or by elucidating the complex and understudied physiology of gonadal hormones. “It is only by understanding what’s occurring after ICH in both sexes as they age, and elucidating the effects their endogenous gonadal hormones are having, that we will have the potential to affect change by modulating that process to the benefit of the patient,” James confirms.