Still many unknowns in his field

If our DNA is like a piece of music, epigenetics is how it´s played

There are many analogies to explain epigenetics. Consider a piece of music. The notes are the same for anyone who plays it. But the sound can be very different depending on the conductor, orchestra or venue. Epigenetics, Lund newcomer Christopher Douse´s field of research, is the study of how that music is played.

By Agata Garpenlind

Congrats on the grant and welcome to Lund and EMV! What does it mean for you and your research?
– Thank you. I am delighted to have the opportunity to work at LU. It's a fantastic environment for my research programme, which integrates tools from genomics with molecular and structural biology.

How will you use the grant?
Along with former colleagues in Cambridge, UK, we discovered a complex of proteins that are essential guardians of the human genome. We found that one of these proteins, MORC2, teams up in pairs and binds our DNA. In doing so, it helps to prevent the replication of pervasive, mobile genetic elements called retrotransposons. This is important to our health: unchecked retrotransposons can cause genome instability, a hallmark of cancer. More specifically, around the same time as we were figuring out its function, clinical reports identified that patients with mutations in the *MORC2* gene have severe inherited developmental disorders. The grants will enable me to start to unpick the function of MORC2 in more detail. We then hope to expand this analysis to other regulators of retrotransposons, and understand how the different proteins talk to each other in the cell. Understanding these biological pathways in molecular detail can generate clinical impacts in two respects: (1) we can unpick what happens when particular pathways go wrong – for example, in neurodevelopmental disease and cancer, and (2) we can identify opportunities for rational drug design.

What´s the amount and where does the grant come from?
I've been supported mainly by SSMF (Svenska Sällskapet för Medicinsk Forskning) in the form of a 4-year large grant. This support is very generous, totalling 1.7M SEK per year until March 2024. I have also recently been awarded 500,000 SEK from Crafoordska stiftelsen for a one-year project.

Your research deals with a field called epigenetics. What´s that?
There are many nice analogies to explain epigenetics. My favourite is to consider a a piece of music. The notes are the same for anyone who plays that piece of music. But the sound can be very different depending on the conductor, orchestra, venue

etc. One can imagine the piece of music is our DNA (or, our genome) - a long sequence of letters. Epigenetics is the study of how that music is played. It refers to how our genome is regulated in ways that do not depend on DNA sequence alone, how gene expression is turned up and down. This is important. It is how we manage to have cells with specialized function. They all contain the same genome, but epigenetic regulation enables (for example) nerve cells to do a very different job to muscle cells in the heart.
There are many, many things we do not understand about our genome, but we pretty much know the sequence of letters now. However, there are even more unknowns about epigenetic regulation. I think we'll be busy for a long time thinking about and studying the open questions.

Please outline the process of the work. What steps does it consist of? What do you do when you go to work?
I would say around 50% of my work is doing experiments at the bench, and 50% at a computer, although this changes. During the pandemic I have been much more computer-based. Such 'dry' work is a mixture of data analysis, grant applications and communicating data through talks and research papers.

What is the biggest challenge with your research?
Connecting observations made in a dish of cells to what happens in a human patient.

What kind of breakthrough do you hope for?
I think what we are missing from medicine is still a deep understanding of the underlying biology. There is so much to discover. My gut feeling is that by discovering basic biology, you uncover new links that can be useful in designing therapeutics or understanding a disease better.

If successful, what might your research mean to patients in the future?
If we understand what the MORC proteins are doing in normal healthy development, we can start to unpick what goes wrong in patients, when these pathways are somehow perturbed.

Which group of patients is it? How will they benefit?
At the moment, the clearest link is between MORC function and patients with genetically-defined developmental disorders caused by mutations in *MORC* genes. Understanding the pathways makes it possible to rationalise the potential pathogenicity of particular mutations found during genetic testing of patients, and give affected families an explanation of what is happening.

Is it possible to make predictions about when?
Therapeutic modulation of MORC function – either using selective agonists or antagonists, or with gene therapies – may have utility in the clinic for treating a diverse range of disorders. Unfortunately it is very hard to predict when that might come to fruition. What's for sure is that we need an understanding of the basic science in order to have the best chance in that regard.

What do you like the most about your job?
Being paid to think - and inspire others to think - about biology. The complexity and beauty of the natural world are astounding.

What are the main trends in your research field right now?
Even though the human genome sequence was 'finished' in 2003, it was just a first draft. Even now, 17 years later, we have almost no idea what the vast majority of genetic information we carry is doing, or how it is processed and regulated. In my field, the biggest questions are: (i) what is most of our DNA, the so-called 'dark matter of the genome' (which does not encode anything), doing there? (ii) what roles does epigenetics play in regulating and protecting our genome during healthy development?

ABOUT

Christopher Douse, researcher, epigenetic regulation of the non-coding genome and its importance to human health

Age: 34
Family: Partner Miya and 3-month old boy Aki
Lives in: Malmö
Education: Master's in Chemistry (University of Oxford), PhD in Chemical Biology (Imperial College London)
Professional background: Postdoctoral Research Associate and then UK government Research Fellow at Department of Medicine, Cambridge University
How did you end up at Lund Uni? I moved to Malmö in January 2019 to be with my partner. I was commuting to the UK, which was exhausting and totally unsustainable. I met up with Johan Jakobsson here at EMV because I had admired his lab's work on epigenetic silencing in the brain, which is closely connected to my own interests. Johan kindly offered advice on the Swedish funding system and suggested I apply for a few start up grants. I did and after many rejections, I was awarded a grant from SSMF
In free time: Playing tennis, swimming in the sea, hiking, cooking, watching a bizarre sport called cricket