How would you explain the main findings of your paper in lay terms?

SK: Glucocorticoids (GCs) are a commonly prescribed anti-inflammatory drug in the clinic that are used to treat a wide array of ailments, including rheumatoid arthritis, asthma and autoimmune disorders. However, despite their therapeutic benefit, high-doses and/or prolonged duration of treatment results in severe side-effects, the most common of which include osteoporosis, high blood pressure and impaired wound healing. There is therefore a need to develop new, potent GCs without the associated negative side effects, prompting a deeper investigation into their cellular activity. This study identified an early role of GC treatment on the structural integrity of cells, causing them to become stiffer and impede their motility. We describe the molecular mechanism by which GCs rapidly inhibit cell migration through the binding of HDAC6 within the cytoplasm, an enzyme responsible for maintaining the stability of the cellular cytoskeleton. This rapid action occurs too early to account for any changes in gene expression, meaning this is a non-genomic action of GCs and implicates HDAC6 as the effector of impaired wound healing seen upon GC treatment. Our findings shed further light on the non-genomic action of GCs and will aid in the design of safer steroids.

DM: GCs are potent anti-inflammatories that have a broad range of therapeutic benefits. However, their clinical application is limited due to an array of severe side effects, such as impaired wound healing and osteoporosis. GCs are known to reduce cell movement, something that can have a beneficial effect, i.e restricting movement of immune cells, thus reducing inflammation; or have an adverse effect, i.e. impaired wound healing. Understanding how GCs control cell movement is important for the design of new therapeutics that have all the benefits and none of the associated side effects. Here, we show that GCs are able to rapidly restrict the movement of cells, by interacting with the enzyme HDAC6. This effect is too fast to be due to a change in gene expression, the classical way GCs are thought to work. Our work describes a previously unconsidered way that GCs can control cell movement, and will hopefully benefit drug design in the future.

Were there any specific challenges associated with this project? If so, how did you overcome them?

SK: We initially struggled to demonstrate an interaction between the glucocorticoid receptor (GR) and HDAC6 owing to its transient/ unstable nature. Consequently, we used fluorescence cross-correlation spectroscopy, a quantitative imaging technique, to monitor the real-time GR–HDAC6 interaction within live cells. We were then able to quantify the increased binding dynamics within the cytoplasm upon treatment with GC.

DM: Logistically, this project was challenging. The project started in my PhD and was carried on in Stephen’s, and continued into our respective post-docs. Team work, good time management and planning were really important in getting this work to where it is today.

Why did you choose Journal of Cell Science for your paper?

SK: We chose the Journal of Cell Science due to the high standard of research it presents, which also suitably fits with our in vitro study predominantly focusing on the cellular effects resulting from steroid treatment.

DM: The Journal of Cell Science’s reputation for publishing high quality and exciting molecular and cell biology is what attracted us to submitting our research here.

What motivated you to pursue a career in science, and what have been the most interesting moments on the path that led you to where you are now?

SK: Science has always been a passion of mine, enough that I have spent considerable time in academia, research institutes and the pharmaceutical industry. My experiences naturally led me to pursue...
postgraduate study and now postdoctoral research. Admittedly it was the decision to uproot and change career paths to start a PhD that ended up being the most interesting moment so far, though I’m sure there will be plenty of surprises left for the future.

DM: The molecular processes that govern how the human body maintains homeostasis, responds to external challenges and sometimes fails are utterly fascinating. Being able to investigate this each day is a privilege. However, life could have been so different, as before I decided to apply for a PhD, I was on the verge of accepting an opportunity to train as an accountant.

Who are your role models in science? Why?

SK: I find inspiration from those that can effortlessly disseminate scientific research, push the boundaries of their respective fields, and aid the education and training of new scientists.

DM: As both a child and adult I have always been in awe of those individuals that could make science approachable, be that in science museums, documentaries or books.

What's next for you?

SK: After completing my PhD, I’ve since taken a postdoc position at the Cancer Research UK Manchester Institute under the supervision of Dr Claus Jorgensen, researching intra-tumour heterogeneity in pancreatic ductal adenocarcinoma.

DM: My PhD saw me study GCs, that as mentioned, are potent anti-inflammatories. After graduating, my focus switched from studying immunosuppressants to researching the innate immune system. First, I worked on NK cells in Prof Dan Davis’ lab, and now I research Alveolar Macrophages in Prof Tracy Hussell’s lab.

Tell us something interesting about yourself that wouldn't be on your CV

SK: When I’m not in the lab you’ll usually find me cycling somewhere around Manchester.

DM: I can make an excellent roast potato.

Reference

High-resolution STED microscopy image of HDAC6, α-tubulin and F-actin expression and co-localisation after administration of the GC dexamethasone. HDAC6 is shown in red, α-tubulin in green, and F-actin in blue. Scale bar: 50 µm.