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CELL SCIENTISTS TO WATCH

Interview with 2021 Hooke medal winner Stephen Royle

Stephen Royle studied Biological Sciences at the University of Sheffield. He then pursued a PhD in the lab of Ruth Murrell-Lagnado at the University of Cambridge, UK, where he investigated the molecular mechanisms of P2X receptor trafficking. In 2002, he joined Leon Lagnado's group at the MRC Laboratory of Molecular Biology in Cambridge for his postdoc to work on synaptic vesicle endocytosis in neurons, and here he also discovered a novel mitotic function of clathrin. Steve set up his lab at the University of Liverpool in 2006, and in 2013 moved to the Centre for Mechanochemical Cell Biology, Warwick Medical School as a Senior Cancer Research UK Fellow; there he has been a Professor since 2019. The Royle lab is interested in understanding molecular mechanisms of membrane trafficking and mitosis. Steve is also on the Board of Directors of The Company of Biologists and the Advisory Groups of Journal of Cell Science and preLights. He is the recipient of the 2021 Hooke medal, established to recognize an emerging leader in cell biology.

Stephen Royle

What inspired you to become a scientist?

One aspect of becoming a researcher is having a scientific mindset; I do enjoy puzzles and have a curiosity about how things work. But career-wise, I kind of got a lucky break to get into research. One of our lecturers, who had links to industry, told us about a research opportunity at a company called GlaxoWellcome, with the option to defer from university for a year. This sounded interesting to me so I applied, but being a bit clueless about what I should include on my CV, I also mentioned that I'm really into music. I learned from the guy who interviewed me that they received hundreds of applications, and one of the reasons he called me in for an interview was that his wife was a musician. They later gave me the job, which is where I got the research bug and decided that I wanted to have a scientific career. I also realized that research in industry wouldn't really be for me and that I needed to get a PhD.

Your first stint into research at GlaxoWellcome was studying Alzheimer's disease. What drew you then to basic research and membrane trafficking?

When I worked at GlaxoWellcome, there was quite a buzz about P2X receptors, which are ATP-gated ion channels, and this sounded like the next big thing. I was actually set on being a neuroscientist at the time, which is why I later went to Leon Lagnado's lab. My first task as a PhD student was to clone a GFP-tagged P2X receptor and express it in neurons. We saw that it was trafficked by the neuron and localized to endosomes, which I ended up studying more carefully and that is how I got into membrane trafficking.

During your postdoc in Leon Lagnado's lab, you discovered a surprising non-endocytic role for clathrin at the mitotic spindle. Could you tell us where you've taken this line of research since starting your lab?

After finishing my postdoc, I had a really clear idea of what I wanted to do in my group, which was to find the binding partners for clathrin on the spindle and understand how it switches from acting in endocytosis to acting in mitosis. But it took a long time to get the lab running; I spent a year applying for money and not doing research during that time, which was really hard for me. Since establishing my lab, we've found that clathrin is part of a complex of probably four proteins at the spindle. We've worked out how the components of this complex bind to each other, and think they crosslink microtubules to stabilize the spindle. We've also revealed some aspects of how this is regulated, and together with the lab of Richard Bayliss, we've been working on solving structures of how the proteins in the complex interact. We are now trying to find inhibitors to break the complex apart, potentially as an anti-cancer approach to stop cells from dividing, but there is still a long way until we get there.

The other angle of your research is membrane trafficking, where your lab works on various projects. Is there one you are especially excited about?

What I'm most excited about at the moment is that we've identified a new kind of transport vesicle called intracellular nanovesicles; this is keeping us very busy because they still need complete characterization. This new discovery has really pleased me because when you work on membrane trafficking, there's so much known already that sometimes you think it's all been done. So I'd encourage everyone reading this to not be put off by working in fields that are well established. We still also work on clathrin-mediated endocytosis, and currently have a project on how chromosomes and membranes interact, which might be important for chromosome segregation and cancer.

Induced relocalisation methods often feature in your work. Why is this technique particularly powerful in answering the types of questions you are asking?

When I started my lab, I really wanted to use these kinds of inducible technologies; however, the grant I wrote on it didn't get

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Steve with his lab (in 2019).

funded. But then, Scottie Robinson developed 'knocksideways' and gave a talk about it in Liverpool. My student at the time, Liam Cheeseman, adopted this method to study mitosis and later actually won the JCS Prize [awarded to the first author of the paper that is judged by the Editors to be the best eligible paper] for that work. We have used this technique a lot, and when my students come up with a question, one of the first things they tend to ask is what happens if we mislocalise a factor. It's a very powerful method, because you can look at a cell before treatment, then 'hit it' and see how it responds immediately afterwards. Therefore, it's often a better method of choice than RNAi or gene knockout. In a recent project I mentioned, where we studied how chromosomes and membranes interact, I was amazed that you can move the ER to the plasma membrane – so it still surprises me what this technology can do.

You already mentioned that it wasn't easy getting your lab running. What advice would you give someone seeking independence?

I think science-wise, the important thing is to find a niche, either for a particular subject or a technique. You also need to develop a style that's your own. I like to think that our lab has a certain style of doing research that distinguishes us from other labs. And related to this, I think the biggest challenge when you're starting out is getting people to notice you and care about what you do. Many PIs who are starting their lab are paranoid about being ripped off and scooped, but actually, a more common problem is just being ignored. Therefore, networking is really important, and there are many ways to do this, including for example volunteering for things or asking a question at a conference. When people find out who you are and become interested in what you are doing, then opportunities come as a result of that. I don't think many new PIs really take advantage of this.

"Many PIs who are starting their lab are paranoid about being ripped off and scooped, but actually, a more common problem is just being ignored."

What kind of researchers do you find inspiring?

I think on the whole, scientists are quite conservative and risk averse. You just have to look at how people behave around the publication process. But actually, as a scientist you do want to take risks and experiment. So, I really admire people that are willing to take a chance and challenge the status quo. I'm also inspired by scientists in highly underrepresented groups, who are up against much more than I am but slug it out every day.

You are a big advocate of preprints, a bioRxiv affiliate who helps screen preprints, and you're also on the advisory group of preLights, the preprint highlighting platform hosted by The Company of Biologists. Where does your passion for preprints come from?

I'm simply frustrated by how long it takes to publish papers, which is on average nine months from submission – this is especially long when you consider that people in my lab are on three-year contracts. Coming in to work on an average day, you'll typically see people in the lab doing revision experiments to get a paper published, PIs writing rebuttal letters and fighting with editors – all instead of making new discoveries – it's a huge time sink. And all of this is happening at a time when we could communicate our findings immediately through the internet. Preprints let you do that and help science go faster, which is why I'm passionate about them. The pandemic really showed this; medRxiv basically saved lives. But also in basic biology, preprints have been driving the fast evolution of fields such as cryo-EM. Of course, peer review is important to a certain extent, and improves our papers, but never materially, I would say.

You run the blog 'quantixed' where, in addition to writing various opinionated posts, you also share some fun coding exercises. Could you tell us a bit more about what's behind this? And have you always been coding?

I've always been interested in coding and have been doing it for a long time at a low level, but I wanted to get better at it. When I moved to Warwick in 2013, I asked for a bit of code that someone in Leon's lab had written, and when I saw it was only a few lines long, I thought that I should have been able to write that. So I decided I'd seriously start improving my coding. This also comes back to the point about finding a niche; I realized that it's quite common in neuroscience for people to code and analyze data in an automated way, but this wasn't so common in cell biology. I started with analyzing small datasets, such as how long it takes to publish papers from my lab, and realized I can do this for the cell biology papers on PubMed and learn how to deal with such a scale of data. I've been documenting and publishing the results on the blog (https://quantixed.org/), and actually some of the posts have had quite an impact. It's been interesting to see the difference in scale by readership; some of the analysis that I put on the internet, which were maybe an hour of work, have been seen by thousands of people, whereas if our lab publishes a paper, it takes months and it will probably only be read by hundreds.

And what lead you to embark on the huge project of writing the text book 'The Digital Cell: Cell Biology as Data Science'?

I wrote a post on quantixed titled 'The Digital Cell', which was a kind of manifesto; I had this idea that I would regularly put up tutorial-type posts showing people how to analyze biological data, and that is what the blog would be about. Richard Sever from Cold Spring Harbor Laboratory Press, who is also the co-founder of bioRxiv, noticed that post and asked me if I wanted to take on

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writing this as a book. I knew this would be a lot of work because some people who have written books warned me that I'd go mad if I did it. But I realized that if I published this book, I would have the chance to change how a lot of people do cell biology – and I like to think it has had an influence and I could contribute something valuable. In retrospect, it would have been a lot easier if I had already been teaching a course on this, as I had to write the majority of the materials from scratch, but I learned a lot and it was fun.

"[…] I realized that if I published this book, I would have the chance to change how a lot of people do cell biology […]"

You are the recipient of this year's Hooke medal. What does this prize mean to you?

It actually means a lot, as it's a recognition of all the people that have been in my lab – I think it's been around 50 over the years, so I just want to say a big thanks to them. I'm not very keen on awards and medals, because they reward the individual for what is a team effort, but when you win one it's a really nice feeling. You also realize that people cared enough to nominate you and then the judges in the committee voted for you. There haven't been many winners outside of the golden triangle, so receiving this medal also shows that you can do good cell biology outside of the leading universities in Oxford, Cambridge and London.

Finally, could you tell us an interesting fact about yourself that people wouldn't know by looking at your CV?

I really love all kinds of music, whether it's free jazz, grindcore, soul or shoegaze. I play the guitar, drums and piano – actually, when I started university I still wanted to be a musician or a music producer, and I was playing in a band. In the end, it was probably a wise choice for me to do research, because the music industry kind of collapsed.

Stephen Royle was interviewed by Máté Pálfy, Features & Reviews Editor at Journal of Cell Science. This piece has been edited and condensed with approval from the interviewee.