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INTERVIEW

An interview with Andreas Prokop

Seema Grewal*

Andreas Prokop is a Professor of Cellular and Developmental Neurobiology at The University of Manchester, UK. His research group studies the mechanisms of axon homeostasis and degeneration, using primary neurons of the fruit fly *Drosophila* as a model system. In April 2022, Andreas was awarded the 2022 British Society of Developmental Biology (BSDB) Wolpert Medal, which recognizes an outstanding individual who has made major contributions to the teaching and communication of developmental biology in the UK. We chatted to Andreas at the BSDB Spring Meeting, where he was presented with the medal, to find out more about his career, his research and his valuable contributions to the teaching and advocation of developmental biology.

Let's start at the beginning, how and when did you first become interested in science?

To be honest, I don't think that I was driven as a young child to go into science. When asked about my professional aspirations, I usually responded: 'director of a zoo'. However, inspired by a highly engaging science teacher at school, I decided to study biology. I started in Bayreuth in Germany for my pre-diploma studies and then went to Cologne. However, I was plagued with doubt about my choice. During a practical course at José Campos-Ortega's 'Institute of Developmental Physiology', I withdrew from the course and found an apprenticeship as a glass painter in a famous workshop in Rottweil.

Unsurprisingly, this triggered intense discussions with my family. Eventually, I reconsidered my options, went back grovelling, and was let back on the course by Campos-Ortega under the condition that I would be tested on all the course materials. This was the first time I properly studied and understood the background information, and I started to take an interest in the course. I was never actually tested, but it was a real eye opener that encouraged me to continue with the studies.

How then did you become interested in neural development and, in particular, *Drosophila* neural development?

During the course, Prof. Pohley (a senior member of the institute) learned of my drawing skills and offered to pay me for illustrating disfigured pupae of the butterfly *Ephestia kühniella* that had been hormone perturbed during development. Gerd Technau worked at the same institute, studying fate mapping of the early *Drosophila* embryo and mechanisms of neuronal fate. He approached me with the view that my drawing skills would make me a good anatomist. I accepted a paid student job in his lab and was tasked with studying the origin of neuroblasts in the larval CNS, which then became the topic of my diploma project. This involved some tricky but amazing experiments in which I took single cells from triple-labelled embryos (genetically encoded lacZ, and injected with HRP and fluorescent dye), transplanted them into unlabelled embryos, video-imaged resultant clones live at the late embryonic stage and, eventually, stained them for HRP and β-Gal in larval brains. It became clear that larval neuroblasts arose from embryonic ones. This was further confirmed using BrdU labelling during my PhD, which I continued with Gerd after his lab had moved to Mainz.

After you completed your PhD, you moved to the UK for a post-doc position, working with Michael Bate in Cambridge. What was the motivation behind this?

It was a mixture of interest and serendipity. Mike Bate was a pioneer in the insect neuroblast field, and I had always admired his conceptual papers. It just so happened that Alfonso Martínez Arias, who worked in the same space as Mike in the basement of the Cambridge Zoology department, came to visit us in Mainz to perform experiments for 2 weeks. During this time we agreed that I would visit them in Cambridge. That's when I met Mike and discussed a project that involved using electron microscopy to study neuromuscular junction formation. At that time, we didn't have all the informative intracellular markers that we have today, and electron microscopy was the only way to look deeper into cells. I found this an exciting prospect and started to apply for fellowships.

I got a Marie Curie fellowship for 2 years and developed strategies to study neuromuscular junctions and muscle attachments in mature *Drosophila* embryos. During this time, I applied for a Lloyd's of London Tercentenary Foundation Fellowship, which required me to write a layman's guide that was understandable to insurance brokers serving on the Lloyd's of London interview panel. When my housemate Mick Gowar, who was an author of

*Author for correspondence (s.grewal@biologists.com)

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children's books, read my layman's guide, he said he felt lost after the first half sentence! We spent several evenings where I organised the beers and he drove me mad with his questions – 'what is cell differentiation?' – and, when I had explained it – 'well why don't you say just that?' It was such a helpful and insightful experience, and statements from that text accompanied me for a long time when presenting talks or writing grants and papers.

After this, you returned to Germany to set up your own research group – what influenced this decision?

It was always clear to me that I would go back to Germany, but it turned out to be quite a challenge at the time. Gerd offered me a position and generously provided me with the freedom to drive my own research. At that time, my group was focussed on understanding synapse formation at neuro-neuronal contacts. This involved innovative clonal analyses in fly larvae, studying the roles of transmitters in development, and adapting primary fly neurons for the task. I got several research grants, obtained my Habilitation (the German university teaching accreditation) and was awarded a Senior Heisenberg Fellowship, which made me a true PI.

After a short stint in Germany, your lab moved to the University of Manchester, where you've been based since 2004 – what triggered the return to the UK?

At the time, many excellent scientists left Germany because the newly created Junior Professorship positions took jobs away from those who had prepared through the slow traditional path. I was encouraged by a former Cambridge colleague, Keith Brennan, to apply for a position in Manchester. There, the whole recruitment process was a fantastic experience – highly interactive, inspiring and so unbelievably quick! I gladly accepted a Senior Lectureship position. Luckily, I could transfer across some of my research grants, which helped me through the dire funding times after the stock market downturn of 2002, and things developed positively from there. Scientifically, it was a 'culture shock' and revelation to suddenly be surrounded by cell biologists and biochemists primarily working on mammalian cell lines. It made me think outside the box and change my rationale for using *Drosophila*: I started using flies to address fundamental biomedical questions that were more difficult to solve in other model systems.

Throughout your career, you've been interested in the cell biology of neurons in development, disease and degeneration, pioneering the use of *Drosophila* primary neurons as a model. Can you tell us more about this work?

Back in Cambridge, I had discovered synaptogenic roles for the spectraplakin Short stop (also known as Shot or Kakapo), a cytoskeletal linker that was curiously identified by three further groups in different functional contexts at the same time! In Manchester, my group studied Shot-deficient primary neurons and we observed severe microtubule curling in their axons. Our studies revealed that Shot mediates the guidance of microtubules into parallel axonal bundles. This led us to the overarching question of how microtubule bundles are maintained long term, meaning 100 years in humans! Using our versatile and efficient culture model, we studied the function of at least 70 genes and observed microtubule curling in a wide range of mutant conditions. By now, our findings have matured into a conceptual model termed 'the dependency cycle of local axon homeostasis' (https://doi.org/10.1002/cm.21657). This model offers novel ways to explain axonopathies and understand why diseases such as Charcot Marie Tooth disease, amyotrophic lateral sclerosis, spastic paraplegia or peripheral neuropathies all have widespread links to genes that can affect virtually every aspect of axonal cell biology; it does not matter where you break the dependency cycle, the outcome of axon decay tends to be similar.

Having worked on *Drosophila* for years, it's no surprise that you're an advocate for using the fly as a model system; you've written lots on this subject (https://poppi62.wordpress.com/publications) and have pushed for increased funding for *Drosophila* research. Is this something you've always felt quite strongly about?

In my opinion, it is important to become an expert in a field before engaging in research in that area. I usually try to write conceptual reviews, which help me to identify the important open questions in the field. I then think about the best ways to address these, ideally using *Drosophila*. Why *Drosophila*? Because it provides me with excellent means to tackle a key feature of biology: complexity. For example, generating a triple-mutant neuron is not rocket science in flies, experimentation takes hours and days (rather than many months in mouse) and does not require a licence. Furthermore, fly maintenance is cost effective: keeping 400 fly stocks in the lab costs £100 per month, whereas the same number of mouse lines would require in excess of £12,000, so fly costs are effectively 0%! Therefore, when considering time and money, failed scientific approaches in fly hurt far less than in mouse and give me the freedom to 'play' with biology, which is enormously satisfying. Our example of studying axonopathies is just one of many examples where fly research delivers new concepts that are of biomedical relevance. The five (arguably six) Nobel prizes in physiology or medicine awarded for fly research speak for themselves.

This said, *Drosophila* is not a mini human, and we must be honest about its limitations. I was once asked on BBC Radio 4's 'Material World' about *Drosophila* research into Alzheimer's disease, and whether we can study personality loss using flies. Of course, that's a very human symptom we can't study in the fly, but we can efficiently address the fundamental and still open question of why nerve cells degenerate in this condition, and our research is a good example. I see it as a waste of time and money if we don't take advantage of non-vertebrate models, such as yeast, *C. elegans* or *Drosophila*, to drive fundamental discoveries in biology that can then be used to inform translational work into mammalian biology.

Drosophila is not a mini human, and we must be honest about its limitations

In addition to pushing for increased funding, you've been involved in promoting *Drosophila* as a model system and as a teaching tool, having set up The Manchester Fly Facility and, as part of this, the droso4schools project. Can you tell us more about these initiatives?

Over the last 14 years, I had always tried to encourage students in their second-year practical course to solve crossing tasks during experimental incubation times. But I soon realised that there were so many concepts they needed to understand. One Easter, I decided not to join my wife and children on their family visit to Spain. Instead, I stayed at home in my pyjamas for 2 or 3 days and began to write 'the fly genetics manual'. I had endless fun and never learned more about *Drosophila*! The manual, which is part of a training package for *Drosophila* genetics, was published in 2013, co-authored with John Roote, and has had enormous success

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worldwide. I believe it to be an important contribution to make sure that newcomers to the field have a realistic appreciation of *Drosophila* as a model system.

A few years before, I had been closely involved in setting up the Manchester Fly Facility with funds from the University and the Wellcome Trust, aiming to generate synergy among all fly researchers at our institute and to make the model accessible to everybody. In 2011, we developed our first outreach activities for a faculty open day. Our strategies and resources were constantly improved over the coming years and eventually were also applied in extracurricular visits to schools. We soon realised that teachers liked to have scientists as role models in their classes but usually took little interest in the actual content we were presenting. So, together with Sanjai Patel – my brother-in-arms for outreach – we supervised placement students and sent them as teaching assistants into schools. This enabled us to engage in true teacher collaboration to develop curriculum-relevant lessons and resources that involved *Drosophila* examples and micro-experiments. In this way, we no longer talk about the fly but teach the curriculum with the fly, so its importance comes naturally to students. Importantly, all our resources are available on our websites and Figshare repositories, where they can develop their own life. For example, we know that teachers across six continents use our materials, our lessons have been translated into Indonesian, Spanish and Turkish, and we have fellow organisations in Turkey, Croatia, Indonesia, Nigeria and Latin America. A key take-home message from our work is the importance of setting objective-driven long-term strategies that can develop momentum and impact.

I see it as a waste of time and money if we don't take advantage of non-vertebrate models

Your contributions to science communication, teaching and outreach have recently been recognized by the BSDB, who awarded you the 2022 Wolpert Medal (https://youtu.be/EUW88IDiZ-A?t=25). Can you tell us what this award means to you?

I was quite lucky that my outreach activities counted towards my promotion in Manchester. But you hear of so many people who invest their personal time in outreach or science communication but do not get any recognition and give up eventually. Our goal must be to allow strategies that promote science as a fundamental pillar in our society. But for this we need reward and the right kind of support. Societies can play their part, and the Wolpert Medal is one important way to achieve this, and I am most grateful and feel honoured to have received it.

But more must happen. For example, funders need to adapt better long-term strategies to support research communities in their efforts to drive science communication over longer time periods towards true momentum – and fundamental research especially needs to urgently be promoted in this way. In addition, we all have to play our part: years ago, I set up an advocacy tab on the BSDB website (http://bsdb.org/advocacy/), which contains important arguments for why developmental biology is important. We all should inhale (and further improve) these arguments so that we can spin them out as elevator pitches whenever there is an opportunity.

Funders need to adapt better long-term strategies to support research communities in their efforts to drive science communication

You've obviously involved in lots of things – research, teaching, outreach, training – but which of these is your favourite?

I especially enjoyed making the 'Small fly, big impact' films (droso4public.wordpress.com/#movies) together with Sanjai and Branwen Messamah, a very talented student. We sat for many hours in my office, turning every word round and thinking about what kind of illustration would be best to use. The films have reached far and wide, and the first one has been translated into Spanish, Indonesian and Arabic, with Portuguese on the way.

I also enjoyed co-organising (with Stuart Allan) the Brain Box event in Manchester in 2016: a science spectacular that attracted 5400 visitors in a single day, with our fly outreach deeply embedded in it (mcrbrainbox.wordpress.com). Our special issue on 'Science communication in the field of fundamental biomedical research', published in Seminars in Cell and Developmental Biology, was also exciting to put together and was a real success, with 55,000 downloads in the first 2 years. Originally, the editors wanted me to edit a cytoskeleton issue, and scratched their heads when I suggested science communication as an alternative topic. But they eventually liked the idea and even granted open access for 2 years.

Finally, is there anything Development readers would be surprised to learn about you?

I guess one thing I've done that might be surprising, and which influenced me a lot when I was younger, was to visit Yemen. I learned Arabic at university for a couple of years and was longing to see Yemen. I went hiking and hitchhiking through the mountains, desert and coastal regions of that most beautiful country that has since suffered so much hardship.