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CELL SCIENTISTS TO WATCH

Cell scientist to watch – Mads Gyrd-Hansen

Mads Gyrd-Hansen studied biochemistry at the University of Copenhagen and received his PhD in 2005 under the supervision of Marja Jäättelä at the Danish Cancer Society Research Centre. He then joined the laboratory of Pascal Meier at the Institute of Cancer Research in London to work on the inhibitor of apoptosis (IAP) proteins. Mads returned to Copenhagen in 2008 to the Biotech Research and Innovation Centre (BRIC) in a senior postdoctoral position with Morten Frödin, and subsequently started his own research group with a career-development fellowship from the Danish Research Councils as part of the laboratory of Niels Mailand at the Novo Nordisk Foundation Centre for Protein Research. In 2013, he joined the Ludwig Institute for Cancer Research at the University of Oxford, where he is now an associate professor and holder of a Wellcome Trust Senior Research Fellowship and a Sapere Aude starting grant from the Danish Research Councils. Mads is interested in the non-degradative functions and regulation of ubiquitylation in pro-inflammatory signalling during innate immune responses.

This article is part of a Minifocus on Ubiquitin Regulation and Function. For further reading, please see related articles: 'Mechanisms of regulation and diversification of deubiquitylating enzyme function' by Pawel Leznicki and Yogesh Kulathu (*J. Cell Sci.* **130**, 1997–2006). 'Exploitation of the host cell ubiquitin machinery by microbial effector' proteins by Yi-Han Lin and Matthias P. Machner (*J. Cell Sci.* **130**, 1985–1996).

Portrait of Mads Gyrd-Hansen.

What inspired you to become a scientist?

I've always been interested in how things work, and I also realised in school that I had difficulties in learning stuff unless I understood the logic behind it. My favourite topics in school were therefore maths, physics and chemistry. Whereas geography, for example where you had to learn the names of countries and so on, I disliked, because there was no logic to it.

What questions are your lab trying to answer just now?

We're interested in how pathogen sensing is translated by the cell into appropriate responses. Our particular interest lies in the ubiquitylation system, in particular how ubiquitin modifications relay the information from a receptor to the nucleus of the cell to drive transcriptional responses. I entered the field through an accidental discovery: during my PhD, I was interested in cell death, so for my postdoc I went to work on inhibitor of apoptosis (IAP) proteins with Pascal Meier. But just before I started, his lab identified a conserved region within these IAP proteins, and we didn't know what this region was doing. It turned out to be an ubiquitin-binding domain and this led us down the path of studying IAPs and ubiquitin, and I just got completely absorbed by the whole ubiquitin system.

Ubiquitin was then emerging as a signalling molecule with many different functions; it must have been an exciting and influencing time?

Yes, no doubt. The work by Zhijian 'James' Chen (UT Southwestern) on the role of polyubiquitin lysine-63 (K63) chains in the pro-inflammatory NF-κB pathway and the fact that ubiquitin chains activate kinase complexes were a huge inspiration. Also, during my postdoc, there were several papers showing that IAP proteins regulate NF-κB signalling, which was based on small-molecule mimetics of Smac, an endogenous IAP antagonist. Then it was shown that X-linked inhibitor of apoptosis (XIAP)-knockout mice are immune deficient and cannot respond appropriately to bacterial infection with *Listeria monocytogenes*. Suddenly, it became very clear that XIAP is not only the caspase inhibitor that everyone thought it was at the time, but is actually a signalling molecule in immunity. This influenced the first years of my own research, focusing on characterising the role of XIAP in the nucleotide-binding oligomerization domain-containing protein 2 (NOD2) pathway.

What do you think makes ubiquitin so powerful and universal as a signalling cue?

One aspect is that ubiquitin is a lot of things. It's a building block to generate polyubiquitin chains and, depending on the linkages, they do different things in cellular signalling. One can almost argue to

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An example of new Nordic cuisine. The first of seven courses Mads was served at the 'Fish Bar' restaurant in Copenhagen.

look at the individual linkages as unique, distinct post-translation modifications. Another aspect is – and we tend to forget this when drawing cartoons of post-translation modifications – that acetylation, methylation and phosphorylation are tiny modifications to a protein, whereas an ubiquitin chain adds a modification to a protein that often vastly exceeds its molecular mass or size. You could go as far as to say the protein substrates that get modified by ubiquitin are just scaffolds to build a new protein – a protein made up of ubiquitins.

What challenges did you face when starting your own lab that you didn't expect?

I think this transition was a bit less daunting than for most other early career researchers, because it was more gradual. When I was in Copenhagen, I could just focus on having a research program. That said, the most surprising or difficult thing when you start your lab – irrespective of doing it gradually or completely independently – is to balance all the duties of a group leader. I had definitely underestimated how challenging this is to do.

How are the challenges that you're facing now different?

Now it's about managing the research portfolio in the lab. Everyone who comes through the lab hopes of course to gain an exceptionally interesting story out of their research. To keep on top of all the projects and to broaden our research interests, that is probably the challenge now – and to balance this with all the duties as a 'citizen' of the research community.

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How do you achieve a work–life balance when you're trying to establish yourself as an independent investigator?

I would say there is no such thing – in my view one should look at being a group leader as being an entrepreneur. You start up your own business, and there is no discussion about the priorities; business becomes your life alongside your family, otherwise I think it is very difficult to succeed. I don't think I'm advanced enough to take the foot off the gas pedal in a sense – I think the priority still has to be research and developing the lab.

What is the best science-related advice you ever received?

One thing Pascal Meier told us was that as a researcher, your biggest asset is trust – in your name, whatever you say and what comes out of your lab. You need to do your best to protect the trust people have in you. Therefore, you need to be as sure as you can that your data is correct, because if people start doubting the things that you publish, then there is no point really in doing research anymore. It is about discovering something that is important and describing it correctly. Your name will always be associated with that discovery, irrespective of whether it is in one journal or the other. If you come out with a paper that turns out to be not correct, that will also stick to your name. Trust is the key thing.

…"your biggest asset [in research] is trust"…

Is this also the most important advice you give to your students or to someone about to start their own lab?

Yes, absolutely. This research area is very competitive and you are certainly pushed to be quick, but to me, it is better to be scooped than to be wrong. One of the things that is a bit unfortunate about the research environment at the moment is that there is huge pressure with regards to deadlines. We are evaluated all the time and in order to get the next set of funding or a promotion, you need to get papers out. People want 'big papers' and big or important discoveries. But there is a misalignment there, because there is a big incentive to do short-term thinking and to get a sellable story out that will resonate with the current fashion, rather than actually thinking a bit deeper about the topic and doing something that will be important. Of course, the two things don't necessarily exclude each other, but there is a tendency towards short-term thinking, which is a bit dangerous in the long run.

What is your advice on establishing good collaborations?

It is again about trust. I try to gauge the collaborators that I have by getting to know them a bit to see how they operate. You have to respect the intellectual contributions of people and let them work on their original ideas and be confidential about what you hear, which is not always what happens. I think as a research community, if we are going to maintain openness and a collaborative atmosphere, which is beneficial for everyone and for society, there has to be a 'gentleman's agreement' about sharing data and collaborating. As a young researcher, I would say do not briskly step into the research areas of other people, and at the same time be fairly open about your work and take the risk, because people will then start trusting you on a personal level in the community.

So you would also advocate being as open as possible to get the most out of the meetings you attend as a young researcher?

Yes, within boundaries, be open and take a bit of a risk. There is also the aspect that when you – especially being new to the field – publish your work it clearly affects the work of other people who have been around for a while. If you have not really engaged with these people before then, in my view, this is not very well received. It is the human factor that we have to remember in research; we all spend a large part of our lives studying a specific topic, and we might be mistaken sometimes, or we might not see all the details. If someone is now moving into the field and is not interacting with you, it can become too much of a competition about who is right, instead of a collegial effort to find the truth.

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In other words, to go back to your entrepreneur image: if you open a new coffee shop on the same street as another coffee shop, it is probably wiser to walk over and shake hands.
That is a very good point, because at the end of the day it is not about beating your competition; it is about working together to create more and make the customer base bigger – if you were a coffee shop. Instead of simply trying to outcompete each other, both shops could gain an added value by actually working together.

Could you tell us an interesting fact about yourself that people wouldn't know by looking at your CV?
I am super enthusiastic about food and wine. I love reading about it, going to tastings and to try new weird food combinations. I really enjoy the recent wave of Nordic cuisine. My oldest daughter is living in Copenhagen and whenever I visit her, we always go out for dinner in an interesting restaurant to taste some new Nordic cuisine. Last year, I was in Japan for the first time and we were taken out to taste classic high-level traditional Japanese food. It was just amazing to experience what they can do with natural ingredients, picked fresh out of the oceans – it was really wonderful.

Mads Gyrd-Hansen was interviewed by Manuel Breuer, Features & Reviews Editor at Journal of Cell Science. This piece has been edited and condensed with approval from the interviewee.