Dr. David Komander
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A ubiquitous paradigm

“In one sentence I could explain what I was going to do, I think that was the breakthrough moment for me. I had my ideas sorted out and it intrigued people, they could see that my plans to tackle the problem could actually work,” says Dr. David Komander.

What Dr. Komander has done, since succeeding in his 2008 interview to become a group leader at the Medical Research Council Laboratory of Molecular Biology (LMB) in Cambridge, is shape a new paradigm in cellular biology.

His unique approach begins with a molecule called ubiquitin. It is found in almost every living cell, its ever-present nature lent to its name. Tiny ubiquitin proteins attach to other proteins, and to each other, to create ubiquitin chains. This process is called ubiquitylation.

Ubiquitin is so versatile it can signal for a protein to be destroyed, send it to another part of the cell, direct it to interact with another protein or stop it from connecting all together. Ubiquitin chains and their interactions ultimately regulate all body functions.

Dr. Komander’s team studies the ubiquitin system in reverse, he explains: “Most people find ubiquitin in a pathway and then work out what it is doing there. We don’t worry about the pathways initially, we just look at the ubiquitin chains and say, ok this is an interesting chain type, but what does it do? What does it bind to? How is it made and un-made? With the proteins to regulate particular ubiquitin signals in hand, we can then link them back to a pathway, revealing new biology the chain type regulates.”

The ubiquitin protein is always the same, but chain construction varies. When Komander started his group it was not clear how complex or specific the ubiquitin system is. His work since has uncovered a complex ubiquitin system at work in every cell: “Many distinct ubiquitin signals exist and they are exquisitely regulated by enzymes,” he says, “when we started, only two types of ubiquitin chains had been studied. But there are eight. We looked at the other chains too. It was daunting because nobody really knew where it would lead.”

The rich diversity of regulation in ubiquitin chains Komander found is now convincing other scientists that the underlying ubiquitin signals could be interesting.

“It’s not enough to say ubiquitin is ubiquitin and there is a ubiquitin chain. That won’t cut it anymore,” says Komander. “We have shown very clearly that different types exist and are differently regulated so we do need to worry about what type of chain is present on a protein. I’m pleased because since our first work on different chain types in 2008 it has really sunk into the field as a new paradigm. Everybody is now looking at what types of chains they have, and the data on new functions is streaming in.”

Links in a chain

To study ubiquitin chains, Komander says you first need to generate the right biochemical reaction. He believes this is why studies on the complexity have initially stalled.

“These ubiquitin chains cannot be easily traced by genomics or proteomics. That’s what makes the ubiquitin system challenging. For twenty years people have tried to understand what proteins do in the cell, what happens when they are mutated or taken away, and what they bind to. None of this can be used for ubiquitin chains because at the basis of their generation is a biochemical reaction that needs to be understood and reproduced, to then enable an understanding of the signal,” he explains.

Hidden marbles

Komander looked back to the roots of biochemistry to try to solve this problem. He has gone through older literature and used developments in chemical biology to find answers. This has led to many new tools and methods to study ubiquitin chains. Most recently, he has used mass spectrometry to take the findings back into cells. “Mass spectrometry is going to be the future and it will benefit from the biochemistry we apply to it, we are working on a way of combining techniques to do this,” he says.

At his first ubiquitin meeting in 2006 it was a sad time for the field. Professor Cecile Pickart, who shaped earlier studies of ubiquitin, had just passed away from cancer. Komander describes how she had been at the prime of her creativity and had asked similar questions to those he and his team have asked since: “A lot of the things we have found build on her legacy. In many cases it was already hidden in the literature as little marbles but nobody put this to good use. We have since opened up the complexity of the ubiquitin system. We and many other groups are now doing experiments to show how different ubiquitin chains play independently from each other.”

New challenges

Komander is now trying to trace links within ubiquitin chains to understand chain architecture. Ubiquitin chains form structures he likens to a necklace: “If you have eight different ways of putting together a chain then that means every little ring in your necklace can potentially receive eight other rings. What you are generating isn’t a chain anymore it’s more like a mesh. We call this a branching chain. It’s not really clear what these branched chains look like or how widespread they are because we don’t have good ways to see them.”

Undeterred, Komander is developing methods to look into branched chains at the moment. “To see chain branching for the first time, that’s one of the next frontiers,” he says.

Industrial collaboration

The progress Komander has made has led to close collaboration with industry. His lab led development of a reagent kit called UbiCREST that other scientists can use to determine what kind of ubiquitin chain they have. It was licensed by Boston Biochem in 2014. “It’s a good method that has had great uptake in the community,” he says, “people can see how useful UbiCREST is. It is very rewarding to develop tools to help other scientists look into ubiquitin systems.”

Structured beginning

Komander's interest in structural work began in Dundee. His PhD was spent between Professor Dario Alessi and Dr. Daan van Aalten's labs at the MRC Protein Phosphorylation Unit (PPU) in Dundee from 2002 to 2005. He spent the previous year working on a diploma thesis in their labs too, having arrived from a biochemistry undergraduate degree in Germany.

During his PhD Komander contributed to a paper that he still counts as a career high: "I think my best paper from this period is not one of my own but is actually the paper where in Figure 1 there's a crystal structure I solved of a mutated protein domain. Then in Figure 2 there's a mouse knock-in of the particular mutant that we structurally characterised. It had a huge impact on me. I think about biology when I see structures, and the breadth of research techniques available at PPU let us do both," Komander says.

Merging fields is a theme Komander carries on in his own lab. In addition to biochemical approaches and mass spectrometry, he has recently started a mouse project to consider how regulating ubiquitin chains affect the whole organism. He says: "I'm excited about incorporating all aspects of biology in the lab. It's challenging because my mind is very structural and I'm not sure I'm ready to become a mouse biologist, but at the same time to be able to do this is really great. I think LMB, like PPU in Dundee, is an environment where you can do these things, where an open minded 'can-do' approach is essential and encouraged."

Of LMB Komander says: "I'm always happy to admit that everyone in my lab is smarter than me. It's exactly the kind of environment I want to be in because I need to be challenged and I want to progress. I love LMB because this is a place where you never lift off the ground simply because every time you do something great and cool and fantastic you just look left and right and realise that all of your colleagues are doing wonderful super-important work too," Komander says.

Thinking time

Moving from his PhD to a post doc at the Institute of Cancer Research in London (2005 - 2008) Komander had the training he needed to be self-sufficient. He describes how close supervision in Dundee taught him to move fast and how to publish a strong paper.

"If as a PhD student you are working in a closely supervised environment I recommend trying to get a post-doc where you have a bit of space," he says. "I worked on a post doc project no-one else was and it allowed me to established a new programme. I knew how to do it and I was ready for it."

Towards the end of his post doc Komander realised that there were more things to do than he could achieve by himself. "I could see a whole field opening up in front of me, it was extremely exciting to be part of it and that's when I realised I really needed to start my own group," he says.

For two weeks Komander stayed at home thinking about how to write a proposal to become a group leader. That was when his ideas about ubiquitin chains transformed from confined projects to an open ended programme.

“When I presented my programme ideas to the LMB, to the division I’m currently in, they were flying. Professor Michael Neuberger hired me, he was a fantastic scientist who could see that this could be a very important area of research and who supported me throughout my tenure. I continue to have great support from many colleagues at LMB.”

Making the most of competition

Having a young family has encouraged Komander to become even more focused and resourceful with his time at work, he explains: “Being able to say no to things is always going to be the biggest problem for any young group leader. No-one teaches you when it’s safe or smart to say no, when you are still trying to build your profile, but it is so important to figure it out.”

Elements of Komander’s work are extremely competitive but he welcomes the competition: “I’m actually quite glad that the competition is so excellent because it means that the things that we publish are independently confirmed by other labs. You can really see progress when lots of people arrive at the same conclusion at the same time. And, when the results differ, it just means we have to work harder and evolve our models to fit all available data.”

“The implications and excitement of what we are doing keep me awake at night, and sometimes, so does the competition. It’s hard to stop when these really competitive things come along and it’s a good thing that my partner is also a scientist and understands when these crunch-times are coming,” he says.

“It is important, though, that the lab does not depend on these super competitive projects. About half the lab is doing completely new things or completely different things which not many people care about but which excite me and my team. At the end of the day it’s essential to focus on the science and not the competition,” he reflects.

“There are many structural biologists who ask beautiful high impact questions about the mechanisms of the biggest machines in the cell, this is fabulous work. I’m very happy to focus on the smaller proteins like ubiquitin and its associated enzymes. Once we figure things out we immediately want to go back into cells and to try to understand how that protein acts at a biological level. That’s what we are trying to do in my lab,” he says.

Final word

Last year Komander went to Dundee twice. He was invited by the PhD students to their symposium and to sit on a PhD viva panel, he says: “Going back always makes me realise how beautiful the Dundee setting is, even though you quickly forget it’s so cold. What was clear from my discussions with the students there is that it is that PPU and the School of Life Sciences is still a fabulous place to begin a research career. I wouldn’t be where I am without my PhD from MRC PPU. There’s not many places that combine amazing scenery with amazing science. Dundee is a place you have to leave in order to see what you had. That’s how I describe it now.”

Career highlights - in Dr David Komander’s own words

- When my postdoc Anja Bremm showed me that she could generate a new ubiquitin chain type, from the proteins we had lying around in the freezer. This gave me confidence that my programme ideas were going to work.

- The time when Tycho Mevissen discovered that each OTU domain deubiquitinase had a distinct linkage specificity. Tycho was a summer student for three months whilst doing this work, and every morning when I came into the lab he had a new result.

- Kirstin Keusekotten, another postdoc in the lab, discovered a new deubiquitinase, OTULIN, following a bioinformatic prediction by our collaborator Kay Hofmann. My jaw dropped when she told me that this enzyme was specific for Met1-linked chains, as this has huge implications for biology, as we are confirming at the moment.

Top publications

1) *Wauer T, Simicek M, Schubert A* and *Komander D*[#], "Mechanism of phospho-ubiquitin induced Parkin activation", **Nature** (2015) Aug 20; **524**(7565): 370-4.

"The work on Parkin is the most competitive project in the lab, and I am happy that we were able to contribute so much to understanding it. It is very exciting and with phosphorylated ubiquitin, this is another emerging frontier that we are getting into at the moment." Dr. David Komander.

2) *Mevissen TET, Hospenthal MK*[$], Geurink PP[$], *Elliott PR*[$]*, Akutsu M, Arnaudo N,* Ekkebus R*, Kulathu Y, Wauer T*, El Oualid F, Freund SMV, Ovaa H, and *Komander D*[#]*,* "OTU domain deubiquitinases reveal mechanisms of linkage-specificity and enable ubiquitin chain restriction analysis", **Cell** (2013) Jul 3; **154**(1): 169-84.

And
Keusekotten K[$]*, Elliott PR*[$]*,* Glockner L, Fiil BK, Damgaard RB, *Kulathu Y, Wauer T, Hospenthal MK,* Gyrd-Hansen M, Krappmann D*,* Hofmann K and *Komander D*[#], "OTULIN antagonizes LUBAC signaling by specifically hydrolysing Met1-linked polyubiquitin", **Cell** (2013) Jun 6; 153(6): 1312-26.

"Here, we discovered that the OTU family enzymes are highly linkage specific. We discovered the first enzymes regulating a number of unstudied chain types. This revealed several global mechanisms of linkage specificity and helped develop UbiCREST," Dr. David Komander.

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3) Komander D[#], Reyes-Turcu F, *Licchesi JD*, Odenwaelder P, Wilkinson KD and Barford D., "Molecular discrimination of structurally equivalent Lys63-linked and linear polyubiquitin chains", **EMBO Rep** (2009), May; **10**(5): 466-73.

"This is my first paper as a group leader, and we show that even very similar chain types can be distinctly recognised and cleaved by proteins. This really showed the specificity in the system, but we only characterised three of the eight possible linkages – this set the goal to add the remaining chains." Dr. David Komander.

Research prizes

May 2014	**Elected EMBO member**.
October 2012	**Recipient of a European Research Council Starting Grant**
June 2012	**Lister Institute Research prize 2012**, awarded by the Lister Institute for Preventive Medicine. This “is awarded to young clinical and non-clinical scientists to help them to pursue their personal research interests in biomedical science or related scientific areas as effectively as possible”. Three new Lister Research Fellows are elected each year. Flexible funding of £200K over five years.
Jan 2011	Elected into the **EMBO Young Investigator programme.**
February 2008	**Early Career Research Award 2009 for Signal Transduction**, awarded by the Biochemical Society. This bi-annual award “recognises the impact of research carried out by early-career scientists who have been awarded their PhD within the last five years”.
September 2005	**Karl-Lohmann Prize** of the German Association for Biochemistry and Molecular Biology (Gesellschaft fuer Biochemie und Molekularbiologie, GBM). The bi-annual prize is awarded for "important contributions in biological chemistry in the PhD or postdoctoral period, to a German scientist under 35".

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This alumni profile was written by Hazel Lambert of sciencestory.com