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CELL SCIENTISTS TO WATCH

Cell scientist to watch – Kevin Corbett

Kevin Corbett graduated in biology and biochemistry from the University of Virginia. He then went to the University of California, Berkeley, to work on the structure and function of DNA topoisomerases in bacteria and archaea for his PhD with James Berger. In 2005, he moved to the laboratory of Stephen Harrison at Harvard Medical School for his postdoctoral work on kinetochore structure and function, particularly the yeast monopolin complex, which promotes proper chromosome segregation in the first meiotic division. Kevin started his own research group at UC San Diego and the Ludwig Institute for Cancer Research in 2011. He received a Sidney Kimmel Scholar Award in 2012. His current research interests include the molecular mechanisms of homologous chromosome pairing in meiosis I, spindle assembly checkpoint regulation in mitosis and meiosis, and how misregulation of meiotic genes can contribute to carcinogenesis.

Portrait of Kevin Corbett. Image credit: Stewart Marcano for Ludwig Cancer Research.

What inspired you to become a scientist?

My interest in biology was first inspired by my high school biology teacher, Mr Dunbar. I have this very clear memory of him standing in front of the class, with his feet rooted on the ground and his arms waving in the air, asking, 'What am I?'. That was his impression of a hydra, a tiny, tentacled fresh-water animal. More broadly speaking, I have always been interested in how things work from a mechanistic point of view, and I probably would have become an engineer if I hadn't ended up in biology. This combination of interests probably explains how I was drawn to structural biology in particular.

What are the questions your lab is trying to answer just now?

We're working primarily on proteins that associate with chromosomes in early meiosis, working out how they organize chromatin and then coordinate programmed DNA breakage and meiotic recombination. This is a very physical process, involving protein assemblies that are essentially chromosome scale. We work on the chromosome axis, which helps to organise chromosomes and to coordinate recombination, and the synaptonemal complex, which assembles between the chromosome axes of homologous chromosomes and is involved in the later steps of recombination. More recently, we've also started working on the spindle assembly checkpoint. Our interest in this pathway started with a shared regulator, TRIP13, that controls both meiotic chromosome axis structure and the disassembly of a critical signalling complex in the spindle assembly checkpoint. Finally, we are looking at the roles of meiotic genes in cancer. Several of the proteins that we study are overexpressed in different cancers, and we're trying to figure out how these proteins could be contributing to carcinogenesis, including a possible misregulation of DNA recombination and cell division.

What attracted you to the meiosis field?

When we started work on the monopolin complex and other meiotic chromosome-associated proteins, there were essentially no labs dedicated to studying meiotic proteins solely from a structural and biochemical point of view. The field had progressed incredibly from the early days of descriptive observations, and there was an essentially complete parts-list for the meiotic program. However, less attention was being paid to assembling these protein complexes and looking at their structures and biochemical functions. This was similar in a way to my postdoctoral field of kinetochore biology – in that field, identification of the huge number of kinetochore components set the stage for current work reconstituting the kinetochore *in vitro* and examining its structure. I'd like to think we'll eventually be able to contribute to the meiosis field in a similar way.

Are you still doing experiments yourself?

Definitely – I try to spend as much as 20 hours per week in the lab when I'm not teaching. I start up new projects, clone things for people in the lab, etc. I find that being in the lab keeps me closer to everyone's projects and primary data in a way that doesn't happen if we just meet in my office.

What has been the most influential publication or work in your field recently?

One piece of earlier work that got me interested in the physical properties of meiotic chromosomes was the description of

Kevin Corbett's contact details: Department of Cellular and Molecular Medicine, University of California, San Diego, CMM-East, Room 2058, 9500 Gilman Drive, La Jolla, CA 92093-0660, USA.

E-mail: kcorbett@ucsd.edu

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Kevin (#27, white) at the 2013 Master's Regionals Ultimate tournament.

something called the beam/film model for meiotic crossovers, by Nancy Kleckner and colleagues in 2004. It deals with the well-known phenomenon called meiotic crossover interference, where meiotic chromosomes form crossovers that are more evenly spaced along the chromosomes and further apart than you would expect by random chance. Nancy's work showed that concepts from materials science could in principle explain this phenomenon, but it's unclear how these concepts can translate to a material like a compacted meiotic chromosome. This is part of the reason that we are trying to outline the structures of both the chromosome axis and the synaptonemal complex, using both bottom-up reconstitution approaches, and more top-down methods like imaging and sequencing. On that subject, we're also very interested in recent advances in electron microscopy (EM); our bread and butter has been X-ray crystallography, but we are working hard to develop EM expertise. This technology bridges the resolution divide between X-ray crystallography and light microscopy, and has the potential to revolutionize our understanding of the meiotic chromosome structure and organization.

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

Finding a balance between writing and lab work is critical when you're starting out. I found that I'm much better at writing in the morning, so it was key for me to start blocking out two to four hours every morning to write. Then I'd do experiments and have meetings in the afternoon. Another big challenge I found was letting go of the little details of every experiment, and letting my people follow their projects to places I would never have thought of.

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

It's really about maintaining the momentum we've built over the last six years: first, maintaining funding as a mid-career faculty member is in many ways tougher than as junior faculty member, where start-up money and early-career grants help a lot to get your lab off the ground. In a similar vein, it's unexpectedly challenging to maintain a core of knowledge and momentum with the level of personnel turnover in an academic lab. Finally, now that we've actually made great progress on a lot of the projects we started in 2011, I'm faced with having to go a little bit more outside my comfort zone to explore new areas and to keep the work fresh. On that subject, I'm fortunate to have brave students in the lab willing to take these steps and develop new projects and techniques, which is hugely exciting.

"Nothing's quite as thrilling as seeing pictures of new protein crystals arrive on your phone"…

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

My wife Mary has been tremendously supportive during the last six years, which has let me focus on the science while making the time I do spend at home count. Another important thing to remember is that your lab still runs when you're off at a soccer game or a dance competition – and I'm always available for a quick consultation by text message. Nothing's quite as thrilling as seeing pictures of new protein crystals arrive on your phone at 10 o'clock in the evening! (*laughs*) In all seriousness: I think that to be a successful scientist you've got to be kind of obsessed with the work. But, I've had to realize that for me, working more doesn't always mean getting more done. I've found that working after the kids go to bed is ultimately less productive than putting the computer away, unwinding for a bit, then coming back fresh the next morning.

What is the most important advice you would give to someone about to start their own lab?

As a junior group leader, you've got to spend a lot of time in the lab because you'll be the best experimentalist in your lab for a good while, unless you're extremely lucky. Don't retreat to your office to write – you need to be working in the lab, producing data and driving the projects forward. Momentum is key! Of course there's the constant need to write grants and papers, and as I said earlier, you have to find those hours in the day when you can write most productively. Further, I'd also encourage new group leaders to get organized from the beginning, which will pay huge dividends when people start leaving your lab. Having those shared strain and reagent databases can help tremendously to avoid duplicating efforts and keeping lots of projects moving.

What is your advice on establishing good collaborations?

It's very difficult to put together a compelling story that spans fields like structural biology, biochemistry and genetics in a reasonable time period as a single lab – especially when you're starting out. Therefore, I feel that the most compelling science emerges when you put together a set of people with different expertise and outlooks on a problem. I've had the most success with collaborations where we've focused on what we're good at, and let our collaborators do the same. An example is our work on HORMA domain proteins with Abby Dernburg (UC Berkeley) – we have a lot of common scientific interests, and at the same time we bring very complementary expertise to the problem. I also think that strong communication – not just at the group leader level but between the students and postdocs doing the work – is very important for keeping a collective work moving along.

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How do you get the most out of the meetings you attend, particularly in the early stages of your career?

Try to see and learn as much as you can at meetings. Early on, you never know where a random piece of data in a poster or talk will let you make that all-important connection that will drive the next big paper. My favorite meetings are the small ones, where you can meet everyone there and dig into what they're all doing in detail. There's always downtime at these meetings, and while it's tempting to retreat to your room and work, I have found that being available, perhaps just working on your laptop in the poster room or something, can lead to a chance encounter that starts a collaboration or a great student or post-doc recruitment.

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

My favourite activity outside the lab is Ultimate (née Ultimate Frisbee), which I've been playing recreationally for almost 20 years now. I usually only get to play once a week, but luckily being in San Diego, it's a year-round sport. A couple of years ago, we put together a team that went to the Masters Nationals tournament in Denver. We didn't win a single game, but it was still a great experience. I find that the ultimate field is one of the only places I never think about science – I'm just thinking about running down that disc.

Kevin Corbett 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.