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INTERVIEW

An interview with James Wells

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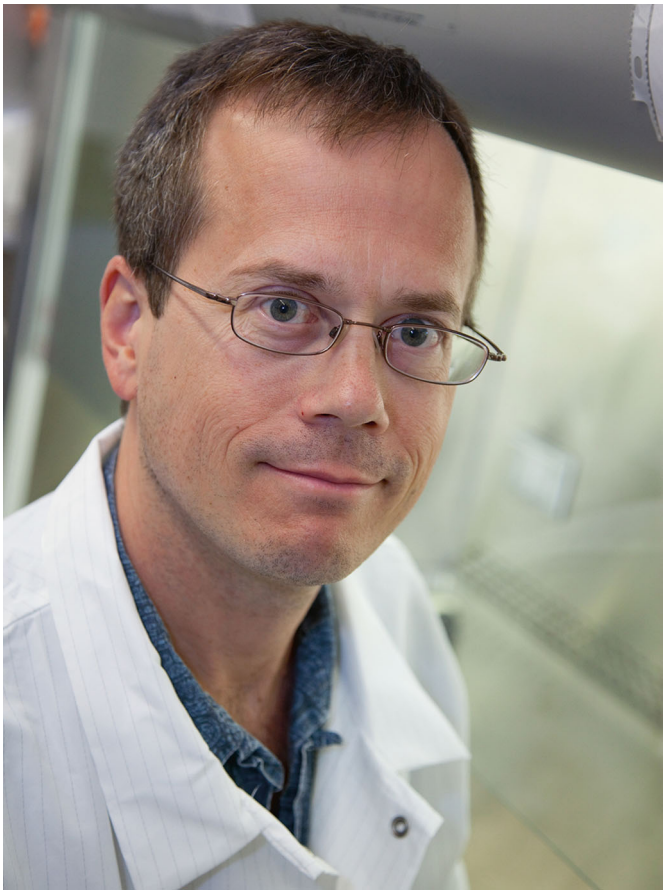
James (Jim) Wells is a Professor in the Division of Developmental Biology at Cincinnati Children's Hospital Medical Center, and Chief Scientific Officer of the Center for Stem Cell & Organoid Medicine (CuSTOM) at Cincinnati Children's. Using both vertebrate embryos and human organoids as model systems, Jim's research focuses on the mechanisms by which gastrointestinal and endocrine organs form. Earlier this year, Jim joined the Development team as an Academic Editor. We caught up with Jim to find out more about his research career, the stem cell and organoid fields, and why he decided to get involved with the journal.



Let's start at the beginning: what first got you interested in science?

I think that, like most scientists, I just have a personality type that is intrinsically curious. I always liked to figure out how stuff works, to the point that I would take things apart and try to put them back together again. Not much has changed in that sense! I think intrinsic curiosity lends itself to the STEM disciplines and I guess having that personality type was the reason I became interested in science.

I gather that you trained as a biochemist – how did you become interested specifically in developmental biology?

I actually trained as a biochemist and molecular biologist right around the time when molecular biology became a discipline. I found the basic concept of molecular and cellular biology – understanding how proteins, macromolecules, DNA and organelles work together in a cell – really exciting. And I think that developmental biology was just a natural extension of that; trying to understand how cells function naturally leads on to the question of how cells come together to make tissues and organs. But, in reality, I didn't get into the field of developmental biology until towards the end of my PhD. At that time, I had been using a cell culture model of muscle cells to understand how they go from single cells to form myotubes and, at the end of my graduate career, I started making transgenic mice to understand how particular genes regulate muscle development and embryogenesis more broadly. So, I think it was that work that got me interested in hardcore developmental biology.

You then carried out a postdoc in the lab of Doug Melton, which I guess is when your 'love affair' with the endoderm began. Why the endoderm?

There was no specific reason, other than I wanted to learn more developmental biology and I wanted to be in a rigorous training environment. I applied to a handful of developmental biology labs to do a post-doc and, obviously, Doug Melton was at the top of my list. And Doug's lab really was brilliant. I liked how he would make us step back from our projects to ask the 'bigger' questions. The trainees in his lab were fantastic too, and I'm still great friends and colleagues with lots of them. So, it was really the training environment that enticed me to Doug's lab and it just so happened that the endoderm was a key focus of the lab. But it quickly became apparent to me that so little was known about the endoderm – how it's patterned, how it's instructed to undergo all these cool morphogenetic processes. When I started my postdoc, virtually nothing was known so I was just there with my eyes wide open and was able to do curiosity-driven research, frankly from then until now.

When setting up your lab, what was the main scientific question that you wanted to address?

I'm not sure there's just one question: I find that there are so many interesting questions! But I think the most exciting thing is to look at the data and follow the most interesting question that's right in front of you. That can take you on an adventure, and often you don't really know where it's going to lead you. So, although I started my lab by looking at how the endoderm becomes regionally patterned along the anterior-

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posterior and dorsal-ventral axis, it quickly became apparent that we could apply these principles of embryonic patterning that were observed in frogs, fish, mice and chicks to direct the differentiation of human embryonic stem cells. But, actually, one of the main reasons for establishing the human pluripotent stem cell cultures was to establish a new research tool. I had always been jealous of 'frog people' because they could grow up litres of frog embryos and do biochemistry and omics-based studies; you just can't do that easily with mouse embryos. But one of the coolest things with differentiated pluripotent stem cell cultures was that we now had dozens of plates of human endoderm that we could do whatever we wanted with. But, of course, as we got more into using the system, we realised that we'd been limiting ourselves by using 2D cultures, and that we should really start thinking about employing other embryonic principles to make more than just a 2D sheet of cells. So, we started to use combinations of signalling pathway manipulations and even combinations of cell types to really explore how we could make organs – or 'organoids' – in 3D *in vitro*. And that all just came from taking the basic concept of differentiation to the next level, which absolutely depends on understanding the embryonic principles of tissue assembly and morphogenesis that drive organogenesis.

Indeed, your studies of endoderm development have been instrumental not only for teaching us more about how this germ layer develops, but also for providing the foundation for directed differentiation protocols that can be used to generate cell therapies from pluripotent stem cells. Do you think this strong link between developmental biology and stem cell biology is sometimes overlooked?

I would agree that, in the early days of directed differentiation, approaches were often empirical; people were adding all sorts of factors into the culture medium to see what happens, and unfortunately that led to a lot of dead ends. I'll give you one great example. A lot of people rushed into the field to make beta cells, with the aim of treating people with diabetes. And a lot of the empirical approaches of just dumping different growth factors into cultures and then looking for insulin expression led to dead ends because, as it turns out, a lot of the insulin-expressing cells that were generated via this approach were, in fact, not real beta cells – they were just cells that made insulin. In fact, in the embryo, there *are* transient insulin-producing cells that never go on to make beta cells. This led a lot of labs, over the course of a lot of years, to make a bunch of insulin-positive cells that were not going to be therapeutically useful. But that was in the early days and I would argue that, now, virtually every successful approach to turn human pluripotent stem cells into a real bona fide human cells or tissues has absolutely followed the playbook established by developmental biologists. The field has certainly evolved and gone back to the basics of embryonic principles. I think that's because the most successful people have been the developmental biologists, whether that's somebody who is making great cardiomyocytes, or someone who's making great organoids – they're all following developmental biology. In my mind, it's reminded us about the continued importance of developmental biology as a conceptual driver.

Your lab has also pioneered approaches for developing gastrointestinal organoids, revealing how pluripotent stem cells can be induced to form various stomach, intestinal and colonic organoids that can be used to model human development and disease. What are the main challenges that this field now faces?

I think for making simple structures, things are probably as good as they're going to be. But making the technology very reproducible, across different labs around the world, is still a challenge. Getting the protocols as simple and robust as possible is the key to translating and transferring the technologies. Even in my lab, when a new person joins it can take a solid 6 months of learning how to make a particular type of organoid, and this requires a lot of hands-on training. So, I think the technical demands will always be a hurdle to a lot of labs that are trying to adopt the technology. The more we can do to make it accessible, the easier it'll be. But that's just for simple systems: once you then add another layer of complexity to that, for example by adding other germ layers or other cell types, things get much more complicated.

Let's take organs of the gastrointestinal tract, for example, since that's what we work on. Basically, to make a gastrointestinal organ you need the progenitors from all three germ layers to come together at the right time and place. Once they do that, you start to see reciprocal inductions, patterning, growth and morphogenesis. We've basically been trying to replicate that concept *in vitro*, for example by making the three germ layers separately and differentiating them into progenitors. Then, once you get the right cells together at the right time, they start to talk to each other and they display a remarkable ability to self-organise. But, building this type of complexity into an organoid, in a robust and reproducible way, is a challenge.

Another challenge is that an academic lab typically doesn't want to spend a lot of time focusing on improving the protocols because they know it's often not going to lead to a snazzy paper, unless it's a huge advance; there's just not much incentive for making user-friendly and robust protocols if you can instead be focusing on the biology or modelling a disease. In a way, it's good that companies are now trying to jump into that space. Having said that, my lab and other labs are still trying to make more user-friendly protocols because we feel it really is a service to the community. At the end of the day, we want to make it easier for anyone to make an organoid.

In addition to running your lab, you are Chief Scientific Officer of the Center for Stem Cell & Organoid Medicine (CuSTOM). What is the main objective of this centre?

The main objective was to build on the strength that we had developed over the past 10 years of using human pluripotent stem cells and organoids to study development and disease. We really wanted to facilitate the use and development of these systems by establishing a core facility and by bringing in new investigators who work on a broad spectrum of organ systems. We've hired four new investigators and are hoping to hire two more this year to branch out to cover more diseases and more organ systems, and to really build a centre of excellence. We've got about 31 investigators in total now, covering lots of different systems. My role has been to focus on the science, for example by bringing in new technologies, by helping to recruit new scientists and by identifying what resources people need to really nucleate an interactive programme. We also want to provide opportunities for people who want to translate their findings into more patient-oriented directions. This meant that we had to set up a seamless infrastructure that allows us to recruit patients, generate patient-derived pluripotent stem cell lines, and make organoids. It's a collaborative initiative that involves basic developmental biologists and clinicians – pretty much everyone's at the table and I think that allows us to do better science.

The Division of Developmental Biology at Cincinnati Children's Hospital Medical Center, which was set up by Chris Wylie (former Editor-in-Chief of Development), has a long and strong history of developmental biology research. Has this environment influenced your career/research?

Absolutely. I mean, who is not – at some level – a product of their environment? The Division, prior to its re-invention as the Division

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of Developmental Biology, was actually the birthplace of teratology. One of the pioneers of teratology, Josef Warkany, who was known as the father of teratology, was based in the division and he studied how environmental factors, such as retinoic acid, can cause birth defects. So, building on that, the division started to recruit a core foundation of people studying the basis of congenital malformations – in other words, developmental biology. The Division then hired Chris Wiley to really build a centre of developmental biology, covering research across lots of species and organ systems. I was one of Chris' earlier recruits – I think I was the fourth person he hired. But the environment that he built has absolutely been essential to driving the intellectual basis of turning stem cells into organoids. Putting a research division in the heart of a paediatric centre was also key; yes, that's been done in other great places too, but it was essentially started here almost 100 years ago, when the Cincinnati Children's Research Foundation was founded in the 1930s. So, this environment really helped to nucleate the collaborations that I have with clinicians, which are absolutely essential for our research programme and allow us to provide a human translational aspect to our research.

You recently joined Development as an Academic Editor – what do you hope to achieve in your new position?

Honestly, I was really honoured to be asked to join the team! As a grad student, I really used to worship the journal, so it was a huge honour for me to be able to get involved. I also felt it was really important to bring the new model systems that we've been developing to other developmental biologists. For me, organoids are just another way to study developmental biology – just another tool in the toolbox – so I really wanted to bring that mentality to the journal. I think that organoids offer a viable new system that really can help enhance basic discovery in developmental biology. Of course, there are many strengths and weaknesses of all model systems. But that's something that people need to consider: which model system is best to address my question? Organoids are good for some things, but not for others, but I do think we can do some really great developmental biology with them.

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What types of papers would you like to see come your way?

Of course, I'd be really excited to see stem cell and organoid papers that are really making an impact and discovering new concepts in developmental biology. But, in general, I think a lot of the most exciting discoveries happen at the junction between two disciplines, and two disciplines that I think really are a marriage made in heaven are developmental biology and biomedical engineering. So, I'd love to see more engineering-based principles applied to studying concepts in developmental biology. For example, there are now some pretty nifty engineering devices that can make gradients or incorporate biophysical parameters, such as flow, into organoid systems. We know that these sorts of physical properties certainly play a role in developmental biology, but they're really hard to study in standard embryonic systems, so I think there's a lot of great engineering-based approaches that can help us to do this. I also think the field has progressed lots in recent years. What's great is that many graduate students are getting trained in both disciplines, so I think they're the ones who are going to really shake up the field as they come up through the system.

Two disciplines that I think really are a marriage made in heaven are developmental biology and biomedical engineering.

What's your advice for young researchers considering a career in developmental/stem cell biology?

I probably wouldn't advise them of anything different than I would have advised them 20 years ago. First, figure out if you like to do research; is this really a passion for you? If it is, then keep doing it until you can't do it anymore, until somebody physically drags you out of the building or fires you! Because if it is something you really want to do – whether you're a technician, a grad student, a postdoc or a PI – then you should give it a try. If you decide at some point along the way that you just don't get enough enjoyment out of research, then that's absolutely fine too as there are hundreds of other great things you can do. But, if you have the brain for research, and if you like doing things again and again (even though they didn't work the last 20 times!), AND if that still gets you out of bed in the morning then you should give it a shot. I know it can be hard – at some point, you might struggle to get grants or to get a faculty position – but pretty much everyone else is in the same boat. You know, I still wonder if I'm ever going to get a grant again. That feeling doesn't go away! The difference is you just know you have to keep at it, if it's what you really want to do.

Finally, is there anything that our readers would be interested or surprised to find out about you?

I actually got my start in research at the University of Maine on a project that focused on wound responses in potatoes. At the time, I thought that was the coolest subject on earth! I couldn't imagine anything better than jabbing a potato full of radioactive label and studying how new proteins get synthesised. I thought it was the best thing ever. Then, I studied brown fat thermogenesis in mice as a technician at The Jackson Laboratory and thought *that* was the coolest thing ever. And then I studied muscle development during grad school at Stony Brook University and I thought *that* was the coolest thing ever. I think you can see the trend…! The bottom line is that it doesn't matter if you're studying wound responses in potatoes or growing mini organs in a dish – you should just be really excited about what you're doing. But, back to the question, I don't think many people know that I got my start stabbing potatoes as an undergraduate research assistant.