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Interview with the Guest Editor – Manuel Théry

Manuel Théry graduated from the Ecole Supérieure de Physique et Chimie de la ville de Paris (ESPCI-ParisTech) and the University Paris Diderot, France, with a master in physics and biology interfaces and subsequently obtained his PhD working with Michel Bornens on the control of cell polarity through adhesion at the Institut Curie, Paris. He joined the French Alternative Energies and Atomic Energy Commission (CEA) in Grenoble, France, where he set up the 'CytoMorphoLab' together with Laurent Blanchoin. Since 2014, Manuel has directed the Paris unit of this laboratory at the Hôpital Saint Louis, where he investigates the (self-)assembly of the cytoskeleton and how this orchestrates cell geometry and mechanical information in the cell. He has won numerous awards, such as the Claude Paoletti Prize and the ASCB Early Career Award, and has been named an EMBO Young Investigator and is an ERC Starting and Consolidator Grant awardee. Manuel is the Guest Editor for the 2019 Reconstituting Cell Biology Special Issue in Journal of Cell Science.

Manuel Théry

What are your research interests?

Cell architecture, cell polarity and how cytoskeleton networks polarise and break their symmetry. Growing is easy, but how does a cell and its cytoskeleton choose one direction to grow? Also, the fact that cells remain as single entities and do not split into many pieces is something I find fascinating. How is it that cells have a singular nucleus? There's a lot of structural control in the cell, and while this may be obvious to many people, it is something I don't find obvious at all. The way for me to address such questions is to look at the architecture of the cytoskeleton and its symmetry breaking. These cytoskeletal networks are permanently renewing themselves, which makes them very different from other types of network architecture – buildings, for example. The cytoskeleton is constantly changing and has to 'think' about mechanosensing, optimisation of forces and weight, and sensors for disassembly and rebuilding, and that's what I'm interested in.

Speaking of cell architecture, boundaries and changing shape – have you ever been tempted to look at the cell membrane?

We're actually now working on the cell membrane. We can make lipid bilayers in micro-patterns with given shapes, add proteins and let actin filaments grow. It's very exciting, but we needed to improve the quality of our lipid bilayers. Lipid biochemistry is very complex and difficult if you want to be in control and do the experiments we would like to do, but we decided to go for it.

So you have a new research direction and a laboratory ('CytoMorphoLab') that is spatially separated, with Laurent Blanchoin being in Grenoble and your group in Paris. How do you organise work – is it all connected, or rather compartmentalised?

We do everything but compartmentalise – everything has to be mixed. Always, always, always. The research group is a bit particular because we have two group leaders, Laurent and myself. It's something that people should think about; it's very beneficial when there are two to lead the team. It helps a lot in solving problems, to think about the big questions in biology, but also regarding organisation and mentoring. When you have difficulties or you feel down being two is always better, and when you have good moments you have someone to be very happy with! It's good to have someone that you can rely on and that's very important. We regularly bring the two groups from Grenoble and Paris together for small meetings and activities where we talk about one specific topic: it could be cell polarity, the centrosome, actin dynamics or something like methodologies. Everyone presents something, even if they're not working on it. It's similar for our annual retreats. We make sure that there is no partitioning of people's skills or their day-to-day projects; we want the opposite. Just like in biology, this mixing takes some energy – otherwise physical chemistry tends to dynamically split things and separates phases. [laughs]

This model has been successful for you, undoubtedly.

The key for the success of our model is that Laurent and I have different expertise – he is a biochemist and I am a cell biologist. Thus, when we discuss things and new projects start, we do not look for specific recognition. We are not fighting over whose idea it was because we know exactly who provides what. It doesn't need to be said. In addition, we are on different pages of our careers, so we are not competing for the same type of recognition. Laurent is very open-minded – he shares a lot, he gives to others and he doesn't keep things for himself and that has made everything very easy.

You say you're a cell biologist, but you didn't exactly start out as one. Where was the starting point for your journey?

The centrosome itself, when I saw an electron microscopy picture of centrioles. In my mind, cells were these globular things where everything is floating around like you see in textbooks. Then, I saw the symmetry in centrioles and I was completely fascinated. How is it that such a structure could exist in cells? I was even more amazed when I heard that the centrioles and the centrosome are at the heart of a radial array of microtubules. At that time, my plan was to become an engineer to build bicycles; I was an intern at the bike company. So,

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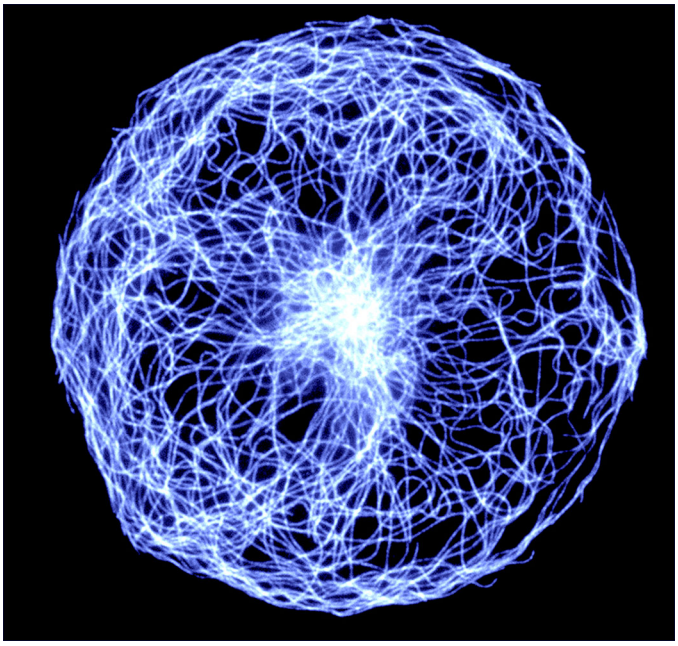

Microtubule network self-centering in enucleated cells on discoidal micro-pattern (Picture by Ana Jimenez).

I was running mechanical measurements on wheels with the aim to improve the geometry and architecture of bicycles. But then I saw these 'biological wheels and spokes' and at the centre something that looked like the hub of the wheel. You have a rotational symmetry to accommodate mechanical forces that are applied on the wheel of the bicycle. I said 'wow!' – life made bicycle wheels! I talked to people at my institution about it and they pointed out to me that Michel Bornens (Institut Curie, Paris), a key figure in the centrosome field, worked just across the street. I sent him an email saying that I'm not a biologist but had a few questions about the centrosome – its position and structure, and whether it was sensing space. He said that's a great idea and that I should do a PhD with him. At that time, I didn't know what a PhD was! This is how it started.

How did you get to work on micro-patterns then?

At that time, Matthieu Piel (Institut Curie, Paris) had just tagged the centrosomal protein centrin with GFP in HeLa cells. Thus, we could record cell shape changes and centrosome position over time and try to correlate how the centrosome position senses cell shape changes. One day, Michel showed me the picture of a 'squared cell' made by Donald Ingber (Harvard Medical School, USA) and argued that our correlations would be much easier to do in these conditions. That was exactly it. I decided to put all my energy into making micro-patterns to precisely measure centrosome position and shape changes.

"…I saw the symmetry in centrioles and I was completely fascinated."

This means measuring a few parameters to answer a simple question and micro-patterns are a DIY story. How do you feel about research that looks at cells or signalling networks as a whole with a complex, big data approach?

That's a really important point. In cell biology, we now have to face complexity, due to the number of components and their manifold interactions. It's a problem of complex networks. It doesn't make much sense now to eliminate one protein and claim one function for it. There are two ways to deal with this: either you embrace it and you take everything into account and you look at the network. Then you have to measure everything: you need well-designed software that will tell you how the network evolves and ways to represent data. It takes hard-core computing, deep learning and clever ways to make sense of these data. That is definitely one way to go. The other way, which I chose, is not the opposite but rather complementary. You reduce complexity and you look at elementary parts of the network. You limit the number of components so that they don't interact in too many ways. You reconstitute elementary functions through *in vitro* assays, adding components one by one. That's what these experiments are good at.

How does the complementarity of reconstitution and big data projects work for your research?

I admit that I was a bit sceptical with regards to being able to make sense out of big data analyses. Then, Reinhard Fässler (MPI Martinsried, Germany) contacted me about his integrin work. In a large-scale approach, his group depleted integrins from cells, re-introduced only one or two different integrins and then compared the composition of focal adhesion sites, generating huge data sets on adhesomes. He contacted me and had predictions from his data – some integrins will lower the adhesion forces despite making larger cell-contact structures, others create very small contact sites but with very strong adhesion forces. His hypotheses were the opposite of the textbook assumptions. We tested this through force measurements and he was completely right. Based on big data, he inferred something that nobody could have predicted. This changed my view of the complementarity of these approaches.

You are very active in sharing and discussing your research on social media and you use preprint servers a lot. In your view, do these measures improve science and the research community?

It gives the possibility for 'open science'. I even feel that it would be great to share data on a weekly basis on Twitter or websites to promote collaborations and unity in research, rather than aiming for self-recognition and stardom. Social media could be used in a better way of course, for example, to discuss data openly and in a more critical way. Also, it can be a distraction because you see so many great ideas and projects floating past you. As for preprints – we put all our manuscripts on BioRxiv now. This is where I'd like my work to be as well in the future. People are invited to comment on the work and to criticise it. There lies the power of preprints for me: you actually have to convince the authors that an experiment you are proposing is valid or worth the effort, unlike an experiment that might be forced upon them during the peer-review process and that doesn't add much insight. This might make the review process more constructive and interesting. I don't need a referee to say yes or no to my work. I publish it and if you suggest an important experiment I'll do it and add it, but if you think the data is wrong then show me the opposite result. The fact that someone's comments will or won't release data to the public makes no sense to me.

A culture of open discussions on preprints and manuscripts could also be a way to recognise a scientist's contribution to the community via their commenting?

Exactly! I think that such a model could promote recognition of people that have not published in the biggest journals but continuously provide valuable comments and suggestions to the community. A junior group leader could thus be highly valued because they spark excellent discussions and come up with

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important ideas. Of course, people like the impact factor because it gives them a metric to select people in a squeezed job market. But we know it is flawed and there are enough numbers to be extracted and measured if you really need numbers to be able to compare. We could come up with numbers that are more personalised measurements of your scientific activity.

Why did you accept the invitation to become a Guest Editor for Journal of Cell Science?

I am very happy that there is a special issue on reconstitution of cell biology and the motivation is to promote the field of research addressing scientific questions with cell-free and reconstitution assays. This Special Issue was a way to shine light on people that have developed very clever approaches and look at cellular self-organisation in specific contexts in a very constructive and instructive way. In the end, it's also about trying to start to build a community on this topic. Dan Fletcher (Berkeley, USA) now organises a subgroup at the annual ASCB on bottom-up biology, so something is starting to form.

What did you hope to get out of this role?

I learned that it's a difficult job because you can't only be kind. If you think a good editor is very kind and nice and accepts all submissions then the issue won't be of high quality. The published manuscripts might not be a fit for the topic or do not bring new information and by doing so, you lower the quality of your issue. This casts a shadow on the field and makes it look less interesting and not very dynamic. So you aim for innovation and quality. A good editor will make fast and firm decisions. The worst is to ask for revisions and to go back and forth many times because the referees are not convinced by the work and as an editor you want to somehow make it work. It leaves everyone frustrated in the end – reviewers and authors, who you have to respect all along the way. I understood this being the Guest Editor for Journal of Cell Science, and now I can also accept editorial decisions on my own research much better.

What was your role in handling manuscripts for Journal of Cell Science?

I read the abstract carefully, I studied the figures and the conclusions and picked a couple of references that were discussed. I checked whether the main conclusions therein related to the conclusions of the manuscript and whether they were similar or different. Based on this, I decided whether to send it out for peer review, or not. And of course I verified whether the manuscript fit into the theme of reconstituting cell biology. Then, you have to choose expert reviewers, which can be tricky when the theme embraces such a variety of research areas. Finally, you handle the peer-review process, the authors' responses to it and you make your decision.

"A good editor will make fast and firm decisions."

When you're not a Guest Editor or doing research, what are the things you do for fun?

When going out or having dinner with friends, I find that discussions with artists are much more enriching and interesting than talking to someone about their big company, big salary job. I'm more and more interested in art, and I find lots of similarities between art and science. Importantly, I'm not referring to finding beauty in a picture, such as in sci-art – I'm not into this at all. The similarity comes with the protocol. By this I mean a scientist and an artist look at the world, ask questions and then find a method to address these questions, to show the problem or illustrate your thoughts. When I look at art, I now don't look at the outcome but I rather think about the design and the implementation of the piece. The only problem is that – a bit like in science – you need to know the field to see how novel or original a specific method is, so a certain expertise is something important to have to understand techniques and, for example, the way art addresses social issues.

Manuel Théry was interviewed by Manuel Breuer, Features & Reviews Editor at Journal of Cell Science. This piece has been edited and condensed with approval from the interviewees.