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SPOTLIGHT

An interview with Hiroshi Hamada

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Hiroshi Hamada is the Director of the RIKEN Center for Developmental Biology (CDB) in Kobe, Japan. His lab focusses on the establishment of left-right asymmetry in the mouse embryo, and the role of cilia in the symmetry-breaking event. Hiroshi's work has been recognised by various awards, including the Keio Medical Science Prize in 2014, and election as an EMBO Associate Member in 2016. We met with Hiroshi on a recent visit to the CDB, to talk about his career and current interests, and the prospects for developmental biology in Japan.

How did you become interested in science generally and developmental biology in particular?

I was interested in science from when I was really young. I don't know why, but I used to like to read science books and in particular I was interested in basic medical science, not in clinical medicine. So I thought I wanted to be a basic research scientist. But my interests in developmental biology are relatively recent. When I started in research, I wanted to contribute to medicine, and because cancer was the most serious disease at that point (as well as now), that was what I wanted to study. But, to start, I thought I needed to get into molecular biology (which didn't really exist as a field at the time), so as a graduate student I studied the structure of RNA – I was a biochemist – and then I learned a lot of cloning techniques when they came along. These were very useful when I moved to the NIH for my postdoc to work on cell transformation, to look at oncogenic mutations.

You first established your own lab in Newfoundland, Canada. How did that come about?

At that time, I wanted to be more independent, so I looked for a job in the USA rather than moving back to Japan. I had a relatively decent publication record and I thought I would have a good chance of choosing where I wanted to go. But I interviewed at several places in the USA and Canada, and Newfoundland was the only place I got an offer.

And how was it there?

It was a wonderful place – the people were very kind and the university was very decent. Most of the people there were more senior and were focussing mainly on education, so they said that because I had a grant I could focus on the research and didn't have to take on other responsibilities. So I was very happy there.

But then you did eventually go back to Japan?

Yes, but that was not my plan. I really enjoyed Newfoundland, but I had two young kids and Newfoundland wasn't the best place to be for their education. So I was planning to move to another university in Canada, where I had an offer. Then my supervisor from Japan called me – he was planning to retire in 5 years, and his associate professor had been promoted and moved elsewhere, so he needed someone to take over from him. I decided to return to Japan, first to Tokyo and then later to Osaka.

How did you find the differences in the science culture between North America and Japan?

When I first moved back, the facilities in Japan weren't as good – even compared with Newfoundland. Now, of course, things are much better here, but at the time all the equipment and so on was quite old. And of course there were huge differences in the culture… I felt almost half-Western by then, so I found it very different when I moved back. Fortunately, my professor ensured that I could do my own research and be independent and kindly assigned the best graduate students to me.

So when did you actually become a developmental biologist?

When I was in Canada, I started working on embryonal carcinoma (EC) cells, and I was interested in differentiation – these cells differentiated very nicely. One of the best EC lines, P19 cells, was established by Michael McBurney at University of Ottawa, and he showed me how to induce the differentiation. So I took that system to Newfoundland, and I tried to answer several questions, such as what determined the undifferentiated state and what triggered differentiation into neural cells.

We tried to identify the genes specifically expressed in undifferentiated cells, and the transcription factors that recognised the undifferentiated cell-specific enhancers. This second approach was very successful – we used enhancer trapping to identify an enhancer active in undifferentiated cells. And then when I came back to Japan, we identified the specific transcription factor that bound this enhancer – which turned out to be Oct4, though we originally called it Oct3. We and two other groups all reported the same transcription factor around the same time; two of us called it Oct3, and Hans Schöler called it Oct4, which was the name that eventually stuck.

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You then discovered Lefty, also in a tissue culture screen, and this led you into working on axis establishment and left-right (LR) asymmetry, which has been your focus for the past two decades. What do you think are the big open questions in the field?

I think we have been able to find out some of the important principles underlying LR axis determination, but there are still many important unanswered questions. For example, we know that fluid flow is crucial – the rotation of motile cilia in the node generates directional flow – but we don't really know how embryos sense this flow. The first molecular asymmetry we see is the degradation of a particular mRNA on one side of the node, but it's not clear how this is induced. Of course, we know that immotile cilia are involved in flow-sensing, but how do they do this? Calcium signalling seems to be involved, but the pathway still isn't clear and this is an active area of research for us.

Another question is what determines the direction in which the cilia rotate, which in turn sets up left versus right. We know there must be inputs from the anterior-posterior and dorsal-ventral patterning systems, and also that there must be some chirality in the system to set up the asymmetry. But there is a lot still to figure out for us to understand why the cilia always rotate in the clockwise direction. Also, it seems like the node cilia are the only ones in the body that rotate as opposed to beat, but why is that?

Your research encompasses a broad range of scales – from the molecular architecture of cilia to the developmental consequences of disrupting LR determination in mice. How do you stay abreast of the latest techniques required to investigate the problem at such diverse levels?

For myself, I think that the question always comes first. I don't think about what I can do with a particular technique, I think about the question and then try to work out what kind of techniques are necessary to address it. And then of course I have to find the people who can use that technique – either through collaboration or people in my lab. Fortunately, I've had good people come to my lab, including people with engineering backgrounds, who've been very good at analysing the flow and the mechanics. I didn't try to recruit them, but they somehow found me, and that's been great.

I understand you've also become interested in mathematical and computational approaches to investigating axis establishment. How do you think such approaches can contribute?

Initially, I wasn't really sure what mathematical modelling or computational science can do for real biology. But I was exposed to the work of my friend Shigeru Kondo, who is interested in Turing patterns and reaction-diffusion models in pigmentation. Then, when I was studying the very dynamic patterns of gene expression during LR patterning, we did lots of experiments but they didn't really get at the principle of what's going on. We thought that reaction-diffusion might be involved, so we decided to try and model it. And this has really helped, and I realised what modelling can do for you. When it works, it really clarifies things in a way that lab experiments couldn't. Personally, I'm not good at mathematics and physics, but I collaborate with people who understand this, and I find it very useful.

You took over as Director of the CDB (probably the most prestigious developmental biology institute in Japan) a couple of years ago, in the wake of the problems with and fallout from the STAP cell papers. How is the institute moving forwards from that difficult period and what do you hope to achieve as director?

Masatoshi Takeichi was stepping down as Director, and partly because I was on the advisory council of the CDB and was familiar with the institute, they asked me if I would take over. And I have a great respect for the CDB and the people, including Takeichi-sensei, and how they run the institute, which has always been very fair. For example, they always make sure to select the best people for positions rather than choosing their friends, which is of course very important. And everything they do is like this. So I knew that this was a very important institute and we couldn't see it run into difficulty or disappear – we had to support it, and I hope I have done that as Director.

I see my job mainly as to rejuvenate things – several people have moved on and we have recruited and keep recruiting some very good new people, so we are looking to the future. One thing we want to do is to extend the scope of the CDB a bit. Traditionally, we have mainly focussed on embryonic development, but we now see development as something that continues through life. And so we want to recruit people working on maintenance and homeostasis – adult stem cells – as well as regeneration and ageing.

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More broadly, Japanese science has a long and prestigious history in developmental biology, and is now at the forefront of stem cell research, which of course depends on insights from developmental biology. How do you see the balance between basic and translational research in Japan, particularly in terms of funding?

Fortunately RIKEN headquarters appreciate the importance of developmental biology and they are committed to supporting the field. But we cannot go on with just basic developmental biology – we have to have a balance between basic and more translational science, and this is sensible. Fortunately for us, Masayo Takahashi, who has pioneered transplantation of induced pluripotent stem cell-derived cells into human patients, is based here at the CDB. She likes to be here because she knows that the basic science is important and that the reason she can do translational work is because of the basic foundations. There has to be interaction between basic and translational science, and that can be a little bit difficult, but we have to make sure we bring these people together and I am trying to promote this.

More broadly, I think that there is a larger proportion of grant money in Japan going to stem cell and other translational research, and basic scientists are having a hard time, but I think that's true everywhere. However, it is essential to maintain the diversity in research, because, as history tells us, big breakthroughs do not always come from top-down projects but from unexpected directions.

What advice would you give to young scientists starting out their career in developmental biology?

Try to find an interesting question, and one that you think is important; then, stick with it, be patient and don't compromise to easier questions. It might take a long time, but I think you have to do

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it. I guess the current situation makes it difficult for young people – who have to publish – so maybe I'm saying something unrealistic. But what I used to do was to have side projects that were maybe easier questions, but always returned to the main theme.

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Away from the lab, what might Development readers be surprised to find out about you?

I very much enjoyed my time in Newfoundland – it was a great place with lots of small fishery towns and wonderful wildlife, and I would love to go back. They have a big Irish population, and I discovered Irish music there, which I really like. The first time I visited, when I went for the job interview, I went to my host's house for dinner. And I could hear some Irish music playing in the background. As a result, I am probably one of the few Japanese people who love traditional Irish music.