Jussi Taipale: For the love of data

Taipale is using genome-wide screens to gather information about the signaling pathways that control cell growth and cancer.

As a child in Finland, Jussi Taipale liked to tinker with electronics. But a missed application deadline prevented him from going to technical university to study physics, which turned out to be a lucky thing for the field of biology.

Taipale went on to study biochemistry and soon conceived a love for growth factor signaling pathways. After finishing his graduate studies on TGF-β signaling (1), he obtained a postdoctoral position in Philip Beachy's laboratory at Johns Hopkins University in Baltimore, where he joined the young field that was then coalescing around the signaling pathway regulated by the soluble protein Hedgehog. Hedgehog binds and inhibits the receptor Patched, thereby allowing the protein Smoothened to signal. Jussi has made significant contributions to the understanding of this pathway (2, 3).

"If you spend several years thinking about a few molecules, you learn to think about things from different directions."

Taipale then returned to Finland, where he's now using genome-wide screens to generate reams of new insights about the inner workings of the cell (4, 5). He dug himself out from under a pile of data to talk with us about his work, which he delightedly describes as "the greatest job on Earth."

MISSED DEADLINE

As a child, what did you want to be when you grew up?

I don't remember exactly what I wanted to be. When I was 10 or 15 years old, I got interested in engineering, computers, electronics, and things like that. Later, when I graduated from high school, I wanted to study either physics or biochemistry. When it was time to apply to universities, there were two deadlines that I should have kept track of. The deadline at the technical university, where I could have studied physics, was a day earlier than the one at the University of Helsinki, which offered a degree in biochemistry. I, of course, got them confused and inadvertently applied a day late for physics. The technical university wouldn't consider my late application and that's how I ended up studying biology.

As a graduate student you studied growth factor signaling. What interested you about that topic?

All multicellular animals need to coordinate cellular growth, and I thought that by understanding how this works normally, we could also gain insights about the cases where things go wrong, for example, when breakdowns in signaling cascades lead to cancer.

But Finland is a small country, and there were very few laboratories where I could study growth factor signaling. My professors at the biochemistry department said that Jorma Keski-Oja's laboratory was hiring people to study TGF-β signaling, and so I joined that laboratory. TGF-β is known to regulate extracellular matrix synthesis. Our main focus was to understand how TGF-β associates with and is released from the matrix.

FROM THE OUTSIDE IN

How did you come to study intracellular Hedgehog signaling as a post-doc?

After I finished my graduate work, I stayed in Finland for a while to wait for my wife to finish her PhD. While waiting, I looked at different growth factors for ideas that I could work on as a post-doc, and I worked for a year or so on vascular endothelial growth factor (VEGF) family signaling with Kari Alitalo. But I felt that both TGF-β and VEGF signaling were already pretty well understood, and wanted to work on something that held greater mysteries. I decided to work on Hedgehog signaling, so I applied to Phil Beachy's laboratory at Johns Hopkins and got a position there.

At that time the whole field was only about six years old, so everything was pretty new. I still had this idea that I should study stuff that happens outside of the cell. But with Hedgehog, it was obvious that there were lots of unknowns about what was happening inside of the cell, so that is what I ended up working on.

Jussi Taipale

Your work with Dr. Beachy really helped move the Hedgehog field forward. Did these advances come naturally to you?

I guess it helps that I had studied signal transduction for a while, so it was a field I could relate to. Also, if you spend several years thinking about a few molecules, you learn to think about things from different directions. Other people had already published work on how they thought Hedgehog signaling would work, but we weren't quite sure it worked that way. So we started from scratch.

We first studied cyclopamine, a plant-derived chemical compound that was shown earlier by Michael Cooper to block Hedgehog signals. We found that cyclopamine blocked the pathway at the level of a protein called Smoothened. But if this protein's activity was increased by mutagenesis, it became more resistant to cyclopamine, resembling what pharmacologists would call an inverse

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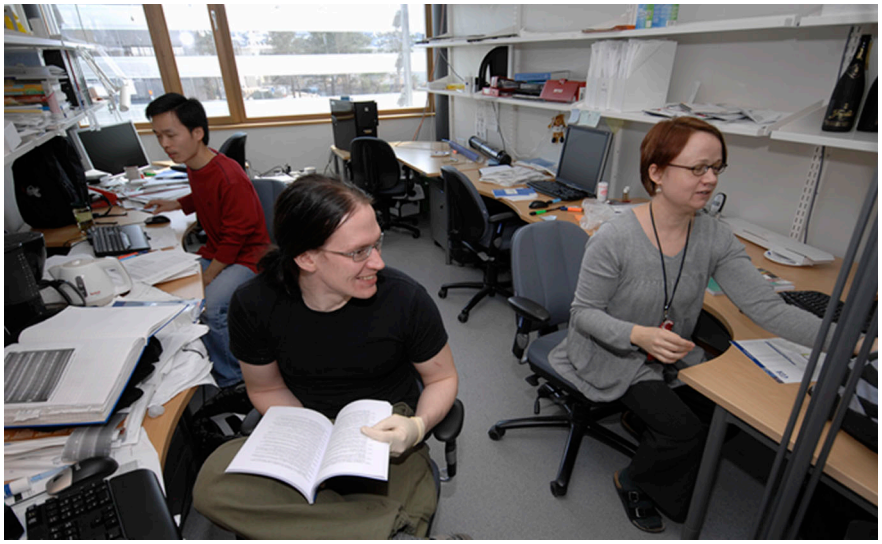

Taipale's post-docs busily sort through the data from myriad RNAi screens.

agonist mechanism. Cyclopamine drives the population of activated Smoothened molecules to the inactive state by mass action—it specifically binds to the inactive protein and locks it in that state. This helped explain how exogenous small molecules like cyclopamine can regulate Smoothened activity. Furthermore, the results suggested that Smoothened activity could also be regulated by endogenous small molecules, and that Patched might serve as a pump for these molecules. It took a while for us to arrive at this model.

Why did you decide to return to Helsinki to start your own laboratory?

Well, I really liked America. My time in Baltimore was very nice, and I would've happily stayed there. But we had two children at the time, and my wife wanted to return to Europe for family reasons.

It would have probably been better for my career if I had stayed in America. The research community there is much larger and it's easier to find people to staff your lab. Here in Helsinki, we have a good department and many strong investigators, but we don't have the same concentration of people as in the States. I get my pick of the top graduate students in Finland, and they are great. But it can be difficult to get others to come here. We have a reputation of being a very cold country, and very far from everything, most of which is not really true. It is cold, but it's not Alaska. It's more like Toronto or Boston, and the research infrastructure and funding here are very good.

Personally, I like the way things work here. Finland is a Scandinavian country with a rather German tradition of how things work. Agreements tend to be held, which makes life simple. And of course, it's a great country in which one can raise a family.

ON THE BRIGHT SIDE

You are using genome-wide screens to study Hedgehog signaling and cancer in your laboratory. What are the advantages and pitfalls of this approach?

When I started my own laboratory, I decided that we would try to focus on growth control and on understanding how signaling pathways drive growth. We have now worked our way to the nucleus, where we try to look at how the expression of genes linked to cell growth is regulated. We start out with a very global approach to identify cell cycle genes and the target genes of signaling pathways. By combining this information, we hope to come up with pathways we can then study in more detail. RNAi screening is a very powerful method for these kinds of global, large-scale approaches.

I've always liked data—I like to have more data, as opposed to less. With these genome-wide approaches, you can come up with a large amount of data in a rather short timeframe, but that's where the problems arise. You can get buried in the data, trying to interpret every little snippet, most of which is just noise in the initial screening. You have to spend a lot of time in analyzing each hit and each gene, and in trying to figure out which ones are real, interesting, and represent novel findings. In this respect, it helps a lot to be computer literate. This work is not something for which many scientists are specifically trained, and I am lucky that my early interests in engineering prepared me for it.

"I think science is a great job, and I really wonder why more young people are not excited about it."

Do you have any words of wisdom for young scientists just getting started in their careers?

I guess the key thing is to do what you are interested in, and keep your focus on the curiosity that will drive your efforts in science. If you start working on something you're not really interested in, then you will most likely fail because you just can't stay motivated. On the other hand, it's also important not to give up. If you don't get excited about fixing failed experiments, then it's going to be difficult to stay in science because 90% of experiments fail. One would do well to remember that on the days when nothing works. Frequently, the problem is not you—it's the experiment.

I think science is a great job, and I really wonder why more young people are not excited about it. Maybe we don't sufficiently promote the fact that it's the greatest job on Earth. JCB

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