Jernej Ule: An RNA runaway success

Ule's got splicing on the brain.

In September 2001, Jernej Ule began his Ph.D. work in Robert Darnell's lab at the Rockefeller University in New York City. Although he undertook an old project that no one expected to turn up anything of interest, Ule soon stunned everyone by turning the endeavor into the premier work in the lab, according to Darnell. The project was to develop a new technique, called cross-linking and immunoprecipitation (CLIP), that would be used to identify the RNA targets of a brain-specific splicing factor called Nova (1).

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Ule quickly repeated his success on a second back-shelf project, in which he used a new type of microarray to identify Nova targets (2). Before leaving Darnell's lab, Ule also developed a bioinformatics approach to predict how Nova regulates alternative splicing (3). From his work, it became clear that Nova regulates a large network of mRNAs, the products of which are involved in remodeling neuronal synapses.

Ule left Darnell's lab just over a year ago to start his own lab at the Laboratory of Molecular Biology (LMB) in Cambridge, UK—one of the most prestigious biology institutes in the world, with one of the most impressive lists of alumni. Far from being daunted by the LMB's prestige, Ule explained in a recent interview that he enjoys being challenged. Perhaps that's why he has a penchant for back-shelf projects.

INDEPENDENT THINKER

How did your scientific journey begin?

When I was in high school I had lots of interests. I was always very driven and running out of time to do what I wanted to do, so I left my decision as to what to study until the last moment.

My parents wanted me to do medicine, but I was very much attracted to art. Biology seemed like somewhere in between. I was always interested in nature and trying to understand life. I thought that the study of life, in a way, was an art of its own.

I didn't like the fact that medicine was a very prestigious subject to study in Slovenia. I wanted to avoid that. Biology was neither prestigious to study nor a good way to get a job, so it was really a decision of my own to study biology. I tended to go my own way whenever possible. Biology was also a bit of an unusual study for boys. It was 80% girls!

What was it like growing up in Slovenia?

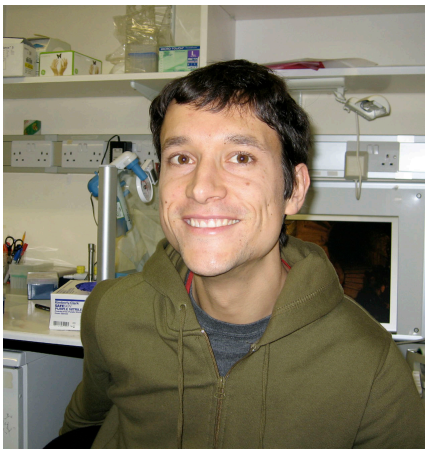
Slovenia has a very good quality of life. I would go mountain hiking in the summers, skiing in the winters, and we had the sea close by. It's a beautiful country. It's in the center of Europe, so you have a good mix of all the different influences from Europe. We would listen to music mostly from the other former Yugoslavian countries and from the Balkans. Our culture is very much linked to that of the Gypsies and Eastern Europe. And it was never a very strongly communist country, it was somewhere in the middle, so we always had the chance to go to Austria or Italy for shopping and so forth.

Slovenia has lots of festivals; lots of people come to visit. It's quite open to the world. I enjoyed it a lot.

FAST LEARNER

After university, you were offered Ph.D. positions at Rockefeller and Cambridge Universities. Why did you choose Rockefeller?

The main reason was that I felt I wasn't experienced enough to study in Cambridge. In the UK, the Ph.D. is very fast. I was advised to study in Cambridge, but I applied in the US to be able to compare between the two options. When I went for the interview at Rockefeller, I was still undecided. But my visit to the campus was completely inspiring. The interview was really well-organized, I could meet and talk to lots of people. And the possibility of doing rotations in different labs was very attractive.



Jernej Ule

I wasn't attracted by New York, per se. I'm not a city person. But at Rockefeller I felt that I could really build up as a scientist, because you have the chance to take classes. And the classes at Rockefeller were totally amazing. Each class, I think, I will never forget. They taught us how to read a paper, how to defend or criticize the same science from different angles. It really makes you develop your scientific thinking abilities. I'm not a person who can just stay in the lab doing experiments day and night. I need to be able to think about it and discuss it.

Cambridge would have been more in-at-the-deep-end?

Yeah. In the UK you choose a lab and start with your research right away. You don't take any classes. If you know already how to think about science, it is a perfect system. But I didn't feel I was ready for that. It would be too big a jump from Slovenia, straight into a very focused lab.

But it seems you developed as a scientist very quickly. Your Ph.D. project was a big success. Tell me about it.

I was working in Bob Darnell's lab with a postdoc called Kirk Jensen, who had been developing a method to UV cross-link an RNA-binding protein to RNA.

Text and Interview by Ruth Williams
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I joined the lab to do the same method with another RNA-binding protein, called Nova. Nova didn't cross-link that well, so my project was to try to improve the technique, to get enough RNA so that we could isolate the specific binding sequences and identify Nova targets.

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It required lots of tweaking at each step. I was really driven, and I spent all the time I had focused on it. It took about half a year to get it to work for Nova. And, since then, I've spent the last five years making additional improvements with help from other members of the Darnell lab. It wasn't a one-off invention. It needs to be tweaked depending on the type of protein you're working with.

YOUNG MASTER

What proteins are you working with now?

Other splicing factors that are highly expressed in the brain. I would like to understand now how splicing factors work in combination in the brain.

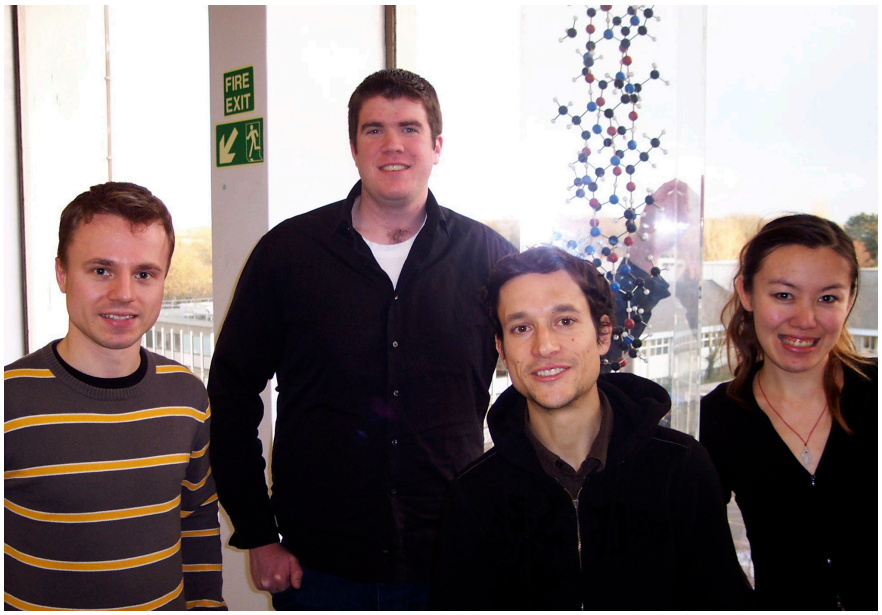
In the past, being just focused on Nova gave you the sense that Nova's really the only factor regulating splicing of its target RNAs in neurons. It's clearly a dominant factor, but it could be a more complex situation once you start looking at other proteins, different brain activities, and different developmental stages.

Why are you particularly interested in the brain?

From our work and that of others, it's apparent that the brain, compared with other tissues, has many more unique splice variants of given genes.

This variability is also seen in other fields, such as transcriptional control and micro-RNAs. The brain is a very diverse tissue. It requires many different cell types and activity responses. So it probably makes sense that it requires the most complex regulation of gene expression.

I'm also very interested in how the brain can encode space and time, how it stores this dimensional information about the environment.



Ule has a new team at the Laboratory of Molecular Biology in Cambridge.

RNA is a very short-term molecule, so it might play a role in giving this time dimension, in terms of gene regulation. It can respond quickly because the transcription step is already done. And, by being degraded quickly, it allows the responses to be time limited.

RNA also allows regulation locally. For example, RNA can be transported to and translated at the synapse, providing a spatial dimension.

Is RNA transport and translation something that you're also interested in?

We're starting to get into using CLIP to study translation and RNA transport. It's a very interesting field. Lots of people have already made big, big steps in it. It's not something that I have worked on in the past, but I think that our method might be able to contribute to it by revealing RNA targets.

After just one year of postdoc work at Darnell's, you were offered a research position at LMB. Was it an easy decision to move there?

Yes. In one way, I wanted to be back in Europe. I've always been attracted by Cambridge. In Europe, it is probably the prime location for science. There's such a concentration of incredible institutes here: the Sanger Centre, the Babraham Institute, the Gurdon Institute.

I feel that I always need to be interacting with other great scientists and to be in a challenging environment. The LMB is a very challenging place. They have a very good tradition, and they try hard to maintain it, so the expectations are high.

Also, I like being in a smaller town. I can bike to work, there's lovely nature all around, and people know each other. It's a place I feel very comfortable with. We've got a small house with a garden. That's something I was missing in New York. I'm very happy to be able to do gardening again. JCB

1. Ule, J., et al. 2003. *Science.* 302:1212–1215.
2. Ule, J., et al. 2005. *Nat. Genet.* 37:844–852.
3. Ule, J., et al. 2006. *Nature.* 444:580–586.