Adrian Liston wins the 2016 Eppendorf Award for Young European Investigators

Presented in partnership with *Nature*

The Eppendorf Award for Young European Investigators was established in 1995 to recognize outstanding work in biomedical science. It also provides the opportunity for European researchers to showcase their work and communicate their research to a scientific audience. *Nature* is pleased to partner with Eppendorf to promote the award and celebrate the winner's work. Science writer Geoff Marsh talks to the 2016 winner Adrian Liston (University of Leuven, Belgium) about his work in elucidating the mechanisms by which the immune system avoids attacking the body while remaining effective against pathogens. To listen to the full interview, visit: **go.nature.com/eyia2016**

About the Award

Adrian Liston is the twenty-first recipient of the Eppendorf Award for Young European Investigators, which recognizes talented young individuals working in the field of biomedical research in Europe. The Eppendorf Award is presented in partnership with *Nature*. The winner is selected by an independent jury of scientists under the chairmanship of Reinhard Jahn, Director at the Max Planck Institute for Biophysical Chemistry in Göttingen, Germany. *Nature* and Eppendorf do not influence the selection. For more information see: **eppendorf.com/award**

Geoff Marsh: Tell me, is now an exciting time to be an immunologist?

Adrian Liston: It's a brilliant time to be an immunologist! We are seeing new tools coming online that allow us to answer questions that just couldn't be answered several years ago. We can now sequence entire genomes of individuals to try to match up the variation in the genome with the downstream. It turns out that when you cannot use one arm of the immune system, the perforin pathway, you end using a different arm — interferon-γ production. Now, when you are excessively activating the second arm, the excessively activated cells can suck out of the system all of a cytokine called IL-2. Unfortunately, IL-2 is essential for another cell type, regulatory T cells, and once you've lost the regulatory cells the entire immune system just starts activating on a massive scale.

GM: And, you've done some work on how regulatory T cells maintain this homeostasis.

AL: Regulatory T cells are crucial for suppressing the immune response. If you have too many, you are going to be immune suppressed. If you have too few, you are going to have inflammatory diseases because you can't stop the immune activation. This means that we really need to have a mechanism that controls the number of T_{reg} cells that are in the system, making sure that we are in this nice 'Goldilocks' zone of not too much and not too few. What we find is that there is a strong feedback loop where extra activated cells drive the production of extra regulatory cells. Conversely, when levels of regulatory cells are too high, the activated arm is shut down, which means that they are also going to be shut down, in turn, by these regulatory loops.

GM: Type 1 diabetes is an autoimmune disease, and your lab has looked at this disease from the angle of the target tissue.

AL: That's right. We used a model of type 1 diabetes, the non-obese diabetic mouse, or the NOD mouse, and investigated the factors that cause diabetes in this mouse. What we found was that if we added stress onto the β-cells — the target tissue of diabetes — the β-cells from a NOD mouse were very fragile, whereas the β-cells from other mouse strains were very robust. Now, this was not immunological in nature, this was really a primary defect of the β-cells. It turns out that in the NOD mouse this is quite a simple genetic trait. There are two genes that are polymorphic in the NOD mouse, which means that the NOD β-cells, when they get stressed, are more likely to die rather than survive, and they are also more likely to undergo senescence because they can't repair DNA breaks as well.

We then wanted to work out whether the same variation existed in humans, and we see again that there is this relationship between islets that seem to be more programmed to die upon stress and islets that were less likely to repair double-strand DNA breaks. One of the exciting possibilities that comes out of this is that if we know that fragile β-cells are a problem, then that is something that we can target. We can design drugs to try to make β-cells tougher. The mouse model we developed is something that we can start using to screen a new class of anti-diabetic drug — this is the first time we have had a mouse model to do this.

GM: Have you any idea what causes us to have weak islets?

AL: Certainly, in the context of the NOD mouse it's a very simple genetic trait. In humans it's probably much more complex. There are a few genes that are good candidates for making islets either robust or fragile, but the other really good candidate is our diet. We know in mice, we can make robust islets fragile by giving the mice more fat in their diet. I think the same thing is probably happening in humans. Certainly, *in vitro* you can cause the same effects in human islets. This also potentially explains the epidemiology of diabetes. It's a genetic disorder, but it is increasing at an exponential rate. How does this happen? The only explanation is that our environment has changed and one of the primary changes in our environment is diet.

GM: Your lab has also looked into the variation in the immune system from person to person.

AL: Yes. Several studies have just come out saying that around 20–40% of the variation is genetic. However, it does mean that about 60–80% is completely unknown and unstudied, because this part of the variation is non-genetic, it's environmental. We set up a study to try to understand what is the environmental driver of variation in the immune system. The way we studied this was to generate an immune-phenotyping platform, which we could use to measure the variation between individuals and then roll out for hundreds of individuals.

GM: So, what factors look to be responsible for the variation?

AL: There are a lot of minor factors that came up: body mass index, sex and so on. These factors made little tweaks to the immune system. One of the biggest factors, however, was age. As you age, your immune system progressively changes. Very young individuals have an immune system that is full of precursor cells that are ready to develop, whereas older individuals have an immune system that is really polarized to a type 1 inflammatory response.

The largest effect that we saw was actually an effect of cohabitation. People in a couple had an immune system that was about 50% more similar to each other than it would be to a random stranger. Remember that genetics accounts for about 25% of the variation, so having 50% of your variation disappear just because you happen to be living together, with no shared genetic background, that's extremely potent.

GM: What is it about living with someone that means that this immune profile is transferred?

AL: I think that when you are living with someone there is going to be multiple different environmental factors that are going to be shared. You're going to be more likely to share the same diet, the same exercise patterns, sleep patterns and stress. You are also going to start to share the same microbiome. The couples that we were looking at had small children living at home. Here, I think the child is going to be acting as a vector to increase the microbiome exchange even further because of course you're changing nappies and you maybe have reduced hygiene levels in the household, and if you have enhanced microbiome transfer, you could imagine that the immune systems are going to become even more similar.

Chair of the Eppendorf Award jury Reinhard Jahn (right) presents the 2016 prize to Adrian Liston.

GM: What are the future directions for your lab? Will you retain this multi-pronged approach?

AL: I think it is very important in science never to get bored and for me this often involves bringing up new topics and exploring new diseases and pathways. But there is a common thread that runs through this. That thread runs through the variation that is present within individuals, how that variation changes our immune system and how the immune system then interacts with the tissue to cause disease. In the future, we want to develop our gene-discovery system, and I'm really interested in how the immune system adapts to the environment of a tissue, as opposed to how it acts in circulation. Often, as immunologists, we think of the immune system as something that can be replicated in a single-cell suspension. Flow cytometry has really revolutionized the way we do immunology, but it does give you the idea that a single-cell suspension recapitulates the immune system. Of course, it doesn't. Immune cells are not present just in blood or in a disorganized tissue such as the spleen. The immune system has to percolate into the tissues, and in the tissues you have anatomical spacing that's important, as well as the relationship of the immune cells with the non-immune cells around it, and for this we need to look at the cells in context, *in situ*, how they are interacting with the organ. This is something that I see as being really important for future research.