Interview with a VENI and Marie Curie Integration grant winner

Dr. Tjakko van Ham recently won two grants: A VENI grant and the Marie Curie Integration grant. The VENI grant provides a maximum of €250,000 to researchers who received their PhD fewer than three years before applying for the grant, and is intended by the NWO to support talented researchers at the beginning of their career. The additional Marie Curie Integration grant is supposed to facilitate the research projects of researchers returned from abroad, and provides an additional €100,000 over a four-year period. Winning these grants has put van Ham in a good position to pursue his research interests, and the BCN newsletter used this opportunity to talk to van Ham to find out more about what these interests are.

Please introduce yourself. What's your background and how did you get to where you are now? Where do you want to go from here?

My name is Tjakko van Ham, I was born in Arnhem and studied at the University of Utrecht (fundamental biomedical sciences/biology). My first research work in the lab (at the Hubrecht Institute), made me decide to go abroad to work for a biotech startup company in San Diego about 10 years ago. Working and living in San Diego really blew my mind, the science is fantastic. Although I worked at a company, it was run mostly by academics who held faculty positions at UCSD, and it felt like a research lab. I went to seminars and conferences across the street at UCSD, the Salk Institute, or the Scripps. You'd see hot-shot professors surfing at six in the morning before work. After this experience, I figured that doing a PhD programme was the next logical step for me, and although I considered getting my PhD abroad, it seemed to me that doing a PhD project in the Netherlands would be best. After that, however, I decided I would definitely return to the US as a postdoc. I wanted to work on functional genetics in the zebrafish, but through a change of fate I finally ended up working on functional genomics in C. elegans. The project involved C. elegans genetics to find new genes in age-related neurodegenerative diseases, with Ellen Nollen (at the time a postdoc in the lab of Ronald Plasterk). Halfway through my PhD, she took an offer from the UMCG for a Rosalind Franklin position and I decided to join. When I was close to finishing my thesis, it was time to choose and visit some labs in the US to join as a postdoc. I had to make a very tough call in deciding on an offer from a well known lab specializing on Alzheimer's and Parkinson's; joining this lab would have been the most logical choice from a career point of view. I finally chose a position at Massachusetts General Hospital in Boston (USA) in a lab, ran by a chemist who pioneered zebrafish chemical screening a little over 10 years ago. Genetics in C. elegans is amazing, but when I heard about his chemical biology approach in zebrafish and had a good experience visiting his lab, I made up my mind. Working in that lab indeed was quite special. I learned more than I could imagine, I had complete freedom in choosing my projects and scientific direction, and I had a great time. In the three years I stayed there, I did the work that forms the basis for my current line of research. That's basically how I got where I am now. What's next? Of course I have a lot of plans, but I bet it's going to look different than I can imagine now a few years down the road. It would be nice if in the next three years I would find out some new biology of how the immune system interacts in the brain, and some small molecules with neat phenotypes, to work out pathways controlling immune responses. On a little longer timeline, I hope I can link some of these findings to mechanisms of brain disease.

What exactly have the grants be awarded for? Can you tell us more about the funded project?

A VENI grant from the NWO is a personal grant to promote scientific talent. They are awarded within three years of obtaining a PhD, and grantees can freely choose

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their subject. The other grant I received is a Marie Curie Career Integration Grant. This European grant allows researchers who worked abroad to continue their own line of research in their home country for four years. The projects are very similar scientifically, although the Marie Curie grant is focused more on the potential for collaborations and networks, local as well as (inter)national etc. The goal for both grants is to investigate how different immune responses, in particular cells like astrocytes and microglia but also macrophages, affect pathogenic processes in the brain. We only came to know quite recently how versatile and important these cells are. It is clear they are involved in many brain diseases, but the circumstances under which they are protective and when they actually can cause harm are unclear. To study this I wanted to really observe how it happens in living brains, and zebrafish are perfectly suitable to do this. Another important reason to use zebrafish is the possibility of carrying out small molecule screens. The lab where I spent the last three years, Randall Peterson's lab at Massachusetts General Hospital in Boston, specialized in chemical biology and drug discovery in the zebrafish. Zebrafish larvae are small enough to swim around in a well of a 96 wells plate, and can live for days surviving on nutrients supplied by the yolk sac. They absorb chemicals dissolved in the surrounding water very well. By using optically transparent plates and automated microscopes you can screen for many different phenotypes, screening up to a thousand chemicals per week. There are many recent examples where this approach yielded small molecules affecting phenotypes ranging from cancer to behaviour. Some of these drugs are very close to testing in clinical trials, a remarkable achievement if you realize they were discovered within the last five years. Part of my proposal is to use small molecular screenings to find new drugs that alter immune cell responses in neurodegeneration.

If I understand correctly, your research involves microscopy in living zebrafish. Can you tell us more about your technique and the insight you hope to gain from this line of research?

Zebrafish develop rapidly; within a day after fertilization they have blood circulation and a functioning innate immune system. Within the first week of development they share the immune cell lineages we have, such as neutrophils and macrophages, but also microglia and astrocytes, very important in the brain. Because they develop an adaptive immune system and T cells a little later, we can use this to distinguish between effects of the two. Because the young fish are transparent, which lets us use different fluorescent proteins to mark different cell types, you can really observe what these cells are doing in the brain, how they interact. To do this we use confocal and multiphoton imaging. Using this "video-microscopy" we can image straight into the brain of anaesthetized young zebrafish without harming the animal. I guess it is not that different from how people who first studied brain diseases literally a century ago spent many many hours behind the microscope peeking into brains, people like Alois Alzheimer. But instead of looking at fixed brain slices, I'm looking at movies of the different cells involved. So in a way a crossover between Ilya Mechnikov, who first observed phagocytic cells alive, and looking at diseased brains.

What I hope to learn is to be able to distinguish different responses of immune cells occurring when brain cells die, and how these contribute to recovery or progression of the disease process. I also plan to carry out drug screens in zebrafish to find small molecules that control such responses. Such drugs will help understand these responses and the effect they have, by acting as a handle to control them. Ideally they would serve as candidate drugs to ultimately treat neurodegenerative diseases. One last thing is, once you have a drug and a cool phenotype, you can identify the target and figure out the molecular pathway. This can take many years, but there are some recent examples from zebrafish where this was done within only a few years…

What do you think sets your project apart from others? What do you think convinced the committee to fund your project?

Zebrafish are more and more often used as a model for biology and medicine, and I'm sure I wasn't the only one including zebrafish in my proposal. I think for me it was important that I had a strong proof of principle; my work from the Peterson lab formed the groundwork for my proposal. Another thing is that in stem cell research and medical fields such as cardiology, immunology, and cancer biology, zebrafish are an established model system with a strong track record of important findings. What I'm doing is a little more novel, but I'm not sure if this worked to my advantage. Figuring out what immune responses do in the brain and whether and how they contribute to disease is still a big question. It's hard to tell why my project was picked, since you don't know the contents of other proposals. Initially, your CV is important of course, for example the papers you published. In fact if you don't spend time working abroad you can really reduce your chances, something I don't always agree with. In addition, you must be convincing and really believe in your research questions and approach. But in the end they want to see potential to bring your own, original line of research to the next level.

■ BY FLORIAN SENSE