Mitochondrial motivation

Name: Lambert Montava Garriga

Career stage: PhD Student

Lambert is a second year PhD student in Dr Ian Ganley's group. He spent his final year as an undergrad in Dundee on exchange from his university in Barcelona as part of the European Union's Erasmus programme. He liked it so much he stayed on for his PhD.

Lambert says: "When first saw mitochondria through a microscope I was really shocked, they are not at all like the simplified drawings in text books. It's a complex network and I just thought wow, this is really cool."

About mitophagy: *One of the ways the cell keeps healthy, mitophagy is the process cells use to get rid of damaged mitochondria. The metabolic reactions that happen in mitochondria provide energy for the whole cell so if they stop working well it's important they are broken down and replaced with new ones. If mitophagy stops working, the accumulation of damaged mitochondria can have toxic effects in cells, leading to cell death and potentially to conditions like Parkinson's diseases.*

Top paper
"Dr Ian Ganley's lab published this paper during my PhD rotation year. It changed my view of mitophagy. It made me realise how much there still is to learn about this cellular process. I also found the numerous possibilities the paper leads to exciting," says Lambert.

mito-QC illuminates mitophagy and mitochondrial architecture in vivo is published in the *Journal of Cell Biology*.

Favourite research tool: The wide-field fluorescence microscope. Follow @mrcppu on Twitter or Instagram to see pictures of Lambert in action in the microscopy suite.

Route to the lab
2013: Research internship, Centre for Genomic Regulation, Barcelona
2014: Research internship, Institut Hospital del Mar d'Investigacions Mediques
2014/15: Erasmus year at the University of Dundee
2015: Research internship in Professor Dario Alessi's lab, MRC PPU
2015: BSc Biotechnology Universitat Autonoma de Barcelona.

My project is to try to decipher the signalling that regulates mitophagy. I'm focused on how cells remove damaged mitochondria and how this quality control mechanism is regulated. If you think about it, cells are full of components and compartments. Each cell is like an extremely messy, busy city. But how do cells decide to clear away one specific part like mitochondria? Which signals do cells use to share when mitochondria have to be removed and how much should be eliminated? These complex signalling mechanisms aren't yet well understood. I'd like my PhD to contribute to answering some of these questions. If we want to figure out mitophagy's implications in human health and potentially develop

new therapeutics, then understanding how it is regulated in cells and tissues is fundamental.

Right now I'm developing techniques that will allow me to study what we call the mitochondrial 'eat me' signature. And, how these 'eat me' signals are regulated. The signals are proteins that mark mitochondria to be eaten by the cell's autophagy machinery. The approach I am establishing aims to identify which proteins are recruited to the mitochondrial surface when it is about to be destroyed. From there, I'll try to figure out which ones are essential to the process of mitophagy. We already know cells have developed self-protection protocols executed by signalling pathways. What we are trying to crack is the emergency pathways that ensure cells remove damaged mitochondria before it is too late.

The potential for what we could do with the tools that Ian is developing is incredible. In 2013 the lab published an assay that measures mitophagy. It's now called the mitochondria Quality Control or mito-QC reporter. Using it we can assess mitophagy both *in vitro* and *in vivo*. It uses two fluorescent proteins that come from jellyfish, one is red and one is green. You can clearly see the colours they make using a microscope and this means you can measure the amount of mitophagy going on. The fluorescence illuminates the entire network of the mitochondria so you can also see its shape. With an assay like this you have so many possible approaches to measure activity. I think we are on the crest of a wave in the sense that now we are going to find out more using this assay. If we want to figure out mitophagy's implications in human health and potentially develop new therapeutics then understanding how it is regulated in cells and tissues is fundamental, my aim is to contribute to that knowledge.

When I joined as undergraduate, I initially did not consider working on mitophagy. After my first rotation with Ian I thought about it so much it prevented me from sleeping. I like the rotation system from the PhD program. It allows you to experiment with different research fields and techniques. I learned a lot, and I had the chance to expose myself to a varied range of techniques such as crystallography, protein purification, in vitro assays or confocal and wide-field microscopy. I think it can help you identify which project suits you the best. It is very important for your PhD. You should research in something challenging and exciting for you. After finishing my rotations, I was just so excited about mitophagy and the capacity Ian had to investigate it I knew it was the field I wanted to work in.

I came to Dundee as an Erasmus student for my final year. The programme was for one academic year, but that felt like a long time to be away from home, so I only committed to one semester. It felt like a bit of an expedition. When I got here I liked it so much that I stayed. The modules for the second semester looked even more interesting and I had the chance to get into the lab again. I ended up doing an internship in Professor Dario Alessi's lab at the same time as finishing my undergraduate and my bachelor's degree thesis. This was the start of my journey in the unit.

My bachelor's thesis was in computational drug discovery. It was a big challenge because it was a whole new field for me. I developed a computational protocol for drug discovery using free software. The thesis was supervised from the university in Barcelona, making

things a little bit more complicated. My supervisor back home was great and helped me a lot. I was lucky that he was happy to talk on Skype. He actually taught me some programming via Skype when I was having difficulties. The module in drug discovery shared by the Drug Discovery Unit here was extremely helpful for my project too. Overall I think it was a wise choice to stay in Dundee for the second semester.

Every day we know more, but at the same time, I realise how much more we still need to know and this makes me want to carry on. Sometimes we assume that because X and Y have been published that's how it is, but it is not always the case. As a scientist, you have to challenge established models to push and further understanding. There is always more to learn. One answer will always lead to multiple new questions.

When I started as an undergraduate, I was mainly interested in research that could be directly applied to treat disease. It can take years for a discovery to translate into a therapy. As time passed, I realised that answering basic research questions could provide a better understanding of how cells and human diseases work. It might not lead to a treatment tomorrow, but somebody could use this new knowledge in the future to develop therapies. If you can understand a problem, then you can fight it, that's my motivation to work in research.

I think being a scientist is a bit like being Indiana Jones. It's like you are trying to find the lost city in a jungle using just an incomplete map and your hypothesis. The hypothesis tells you which way to go, and then you have to figure out a method, or an experiment, that will get you there. Sometimes it gets complicated, and you get lost, sometimes you will never find the city and then your hypothesis might change to 'the lost city never even existed'. Eventually, you will always find a result. However, when you find this 'lost city' and your hypothesis is confirmed with consistent and positive data it is pure adrenaline. You almost feel like Neil Armstrong in the moon!

As told to Hazel Lambert

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