


PEOPLE & IDEAS

Michael Lazarou: Building a body of research

Marie Anne O'Donnell 

Lazarou investigates the relationship between mitochondria and autophagy.

Michael Lazarou was born in Melbourne, Australia, to Cypriot parents who sent him to Saturday school to learn to read, write, and speak Greek. Many words used in science are derived from Greek, so these early lessons may have been useful when Lazarou encountered terms such as “autophagy,” from the Greek for “self” and “eating.” Lazarou was always interested in understanding how things work and says, “A lot of my childhood was spent pulling apart brand new toys to see how they worked, and then reassembling them. Unfortunately, the reassembly was often unsuccessful, resulting in a pile of nonfunctioning toys.” Understanding how damaged pieces of mitochondria are dismantled by the selective autophagy pathway of mitophagy was Lazarou’s main focus during a very productive period of postdoctoral research with Richard Youle at the National Institutes of Health in the United States. Since returning to Australia and starting his own group at Monash University in Melbourne, Lazarou has shifted his focus to understanding the very early stages of autophagosome biogenesis.

We contacted Lazarou to find out more about his scientific journey so far.

What first sparked your interest in mitochondria and autophagy?

The first time you see fluorescently labeled mitochondria in live cells under the microscope you think, “Wow!” They are constantly on the move, dividing, fusing, moving from one location to another. Among all the commotion they are generating energy vital for life. The incredible nature of mitochondria and an inspiring lecturer, my PhD supervisor and now mentor and friend, Mike Ryan, were behind my research focus on understanding mitochondrial biology. Mitochondria are not

only life givers but also killers. Cells have evolved several mechanisms to keep mitochondria happy and healthy. Maintaining mitochondrial health plays an important role in human disease in which mitochondrial dysfunction can cause neurodegeneration. Pioneering work from Richard Youle’s laboratory, driven by Derek Narendra, led to the discovery of a mitochondrial quality control pathway driven by the Parkinson’s disease factors PINK1 and Parkin. I contacted Richard about a postdoctoral position in his laboratory and he gave me the challenge of solving how PINK1 senses mitochondrial damage. My background in mitochondrial biology and protein transport led me to a hypothesis of how PINK1 senses damage. I had the privilege of joining Richard’s laboratory to explore my hypothesis and other ideas about the PINK1/Parkin pathway. The elegant way in which PINK1 senses damage has stood the challenge of scientific rigor (1) and remains one of my best ideas to date. What followed was a rollercoaster ride of exciting discoveries in Richard’s laboratory (2, 3) that led to my growing interest in autophagy pathways and ubiquitin/ubiquitin-like-mediated signaling (4, 5). PINK1/Parkin mitophagy is a rich field of study that combines cell biology and biochemistry of membranes, protein and lipid trafficking, posttranslational modifications, and signaling networks all centered around my favorite organelle, the mitochondrion.

What are you currently working on and what is up next for you?

There are various projects currently being undertaken in my laboratory focused on different aspects of mitochondrial quality control. One of these is on understanding how autophagosomes form around damaged mitochondria. I am very excited about our



Michael Lazarou.

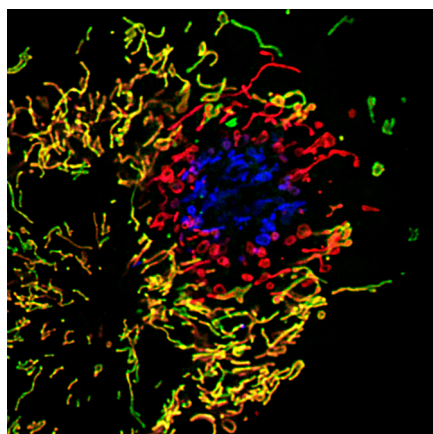
developments in coupling light and electron microscopy with machine learning to generate 3D volumes of autophagosome intermediates. In the future, I would love to generate a video simulation of autophagosome formation during mitophagy that is based on 3D biological datasets from all stages of autophagosome formation.

What kind of approach do you bring to your work?

I try to base my scientific approach on what I have been taught from my mentors Mike Ryan and Richard Youle: to be rigorous, ethical, and reproducible. I aim to honor their ethos by producing research they would be proud of. In addition, whenever possible, I aim to take out the human element of subjectivity when assessing experimental data. We remove subjectivity by developing methods in which computers measure biological outcomes, and this takes

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Mitochondria fluorescently labeled with biomarkers after photodamage with 488-nm wavelength blue light: healthy mitochondria (green and yellow), moderately damaged (red), and highly damaged (blue). Image courtesy of Benjamin Padman.

away unconscious bias. Broadly speaking, I try to embrace new technologies that give robust answers and that help us address questions that couldn't be answered before.

What has been the biggest challenge in your career so far?

I have experienced many of the challenges that I think are common for all researchers in the early stages of their independent careers. Rather than focusing on those challenges, I want to touch on a personal challenge. That is the challenge of dealing with the uncertainty of my future in science. I think more and more of my colleagues in Australia working in basic science are also experiencing the same challenge. Tenured positions are a rarity in Australia, with many researchers depending on grants for their salaries in an environment where funding levels for basic science are tumbling. In response, one of our major medical research funding bodies, the National Health and Medical Research Council (NHMRC), has completely overhauled the system to help improve funding rates. It is well intentioned, but no system can fix the underlying problem of a chronic lack of funding and an apparent disinterest in basic science. Whether this disinterest comes from the NHMRC or the government is unclear to me, but it is notable that the government has also cut funding to the Australian Research Council, an important source of support for fundamental research. I think the pursuit of instant gratification and

single revolutionary projects has put basic science in the backseat in preference for clinical and translatable research that can have easy to measure outcomes. To be clear, I think clinical and translational research is important, but it should not come at the cost of basic science.

Thus, the biggest challenge I face is establishing myself in a new funding system in which no one is sure how to navigate, in an environment of rapidly falling support for basic science. This environment influences my research strategy and forces short-term thinking. How can one plan for big ideas when they cannot be sure if they will still be in their position in the next couple of years? My female colleagues face even greater challenges in a new system that to date has failed to be equitable (6). I am proud that our recent Nobel Prize winners in physiology or medicine have used their influential voices to support the importance of basic science and the role it plays in human health. The medical benefits of basic research into CRISPR-based prokaryotic immunity may not have been clear immediately; however, the utility and medical impact of CRISPR/Cas in editing the human genome is not in doubt today.

"Finding Nemo's Dory summed it up nicely when she said, 'Just keep swimming.'"

What is the best advice you have been given?

My high school class was involved in a development training course and one of the games that has stuck with me my entire life was called "win as much as you can." In this game, you held your partner's hand. If you could force their hand to touch their thigh you would get one point and conversely if your partner could force your hand to touch your thigh, they would get one point. My best friend and I didn't want to compete with each other, so our scores were 0-0. When the teachers asked others in the room for their scores, some were 200-50, others were 22-160, but some were 500-500 and 600-600. Let me remind you the name of the game: win as much as you can. This is a perfect analogy for how we should conduct our research, as only by working together through collaboration can we achieve or "win" the most. I try to share my reagents and

expertise as much as possible in the hope that others will do the same so we can push the boundaries of what we can discover about our world.

What do you enjoy doing outside of the laboratory?

My one persistent hobby has been working out at the gym. It is a great feeling to take your frustrations out on heavy weights after a tough day of science. I still play video games and enjoy reading fictional novels. I also love working on my cars. I currently own the last of the Australian-built Holden SS Commodores. It is an iconic Australian-built car that has a loud and thirsty V8 engine, and production of them ceased permanently in 2017.

Any tips for a successful research career?

Persistence in science is the key to success. Individual big wins or big losses do not define you. It is what you achieve over an extended period of time that matters most. You have to keep fighting toward your goals and let your excitement about understanding how life works drive you. I think Finding Nemo's Dory summed it up nicely when she said, "Just keep swimming."

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Lazarou and his wife Elizabeth enjoying the sunshine at a winery in Byron Bay, New South Wales.