

Interview with the Guest Editor – James Olzmann

James Olzmann did his undergraduate studies in biology at the University of Michigan, USA and subsequently obtained his PhD working on pathogenic mechanisms of DJ-1 in Parkinson's disease, under the supervision of Lian Li and Lih-Shen Chin at Emory University School of Medicine, Atlanta. For his postdoc, James joined the lab of Ron Kopito at Stanford University in 2007, where he studied different aspects of the ER-associated degradation system; through this research, he then became interested in and started working on lipid droplets. James set up his independent research group in 2013 at University of California Berkeley, and since 2019 he has been an Associate Professor. He is also an Investigator at the Chan Zuckerberg Biohub. His lab employs a combination of systems biology, chemical biology and cell biology strategies to understand the mechanisms that govern organelle and lipid homeostasis in health and disease. James is the Guest Editor for the 2022 Cell Biology of Lipids Special Issue in Journal of Cell Science.

What are your research interests?

My lab studies the cell biology of lipid homeostasis, and we have two primary interests. First, we are exploring the biogenesis and regulation of lipid droplets, which are neutral lipid storage organelles that were under-studied for a long time; they were initially thought to be simple inert fat globules in cells, but we now recognize them as bona fide dynamic organelles. They really function as hubs of lipid metabolism and have been connected with a wide variety of pathological conditions, ranging from metabolic disease to neurodegeneration to cancer. The second interest of my lab, which developed more recently, is around lipotoxicity, lipid damage and a form of regulated cell death called ferroptosis, which involves the overwhelming accumulation of oxidatively damaged lipids. We are looking into the connection between ferroptosis and pathological degenerative conditions, as well as the potential to trigger ferroptosis as a cancer therapeutic strategy. I think this field offers an excellent opportunity for us to understand basic mechanisms of how cells maintain lipid quality and prevent lipid damage.

Your core interest is understanding basic mechanisms, but do you ever see your main focus turning to translational research some day?

I think it's interesting how our research develops as academics; my research has followed different tracks and taken me in different directions. My primary drive has always been about fundamental principles of cell biology, and this is what really keeps me up at night. But certain parts of our research, such as our research related to lipid droplets in fatty liver disease and ferroptosis resistance mechanisms in cancer, lend themselves to translation. There's a possibility that targeting some of the factors that we've discovered could be therapeutically viable. I don't see myself becoming completely a translational biologist, but I think when



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possible, exploring those angles has a lot of benefit. Recently, here at UC Berkeley, they've developed a drug discovery centre with a small-molecule library screening facility, so we have a nice pipeline that leverages our genetic screening platform around the cell biology of lipid storage and ferroptosis; as we define factors that regulate these processes, we can use chemical screens to target them. And we'll see, through collaboration, if these efforts will translate into preclinical models and hopefully into the clinic.

You mentioned that your research has taken you into different fields; tell us how you got interested in lipid droplets.

My graduate work was in neuroscience around protein quality control and Parkinson's, and this led me to my postdoc with Ron Kopito, where I was studying how proteins are degraded in the early secretory system via a process known as ER-associated degradation (ERAD). We were doing systems-level studies to understand the organization of functional protein interaction networks of the ERAD system, and, during some control experiments, we unexpectedly observed that a subset of these factors also localized to spherical structures in the cytoplasm; we had no idea what they were and so just called them 'cytoplasmic Cheerios'. It took us a little while to figure out that they were lipid droplets. I became fascinated with these structures and the rest is history. I was fortunate that Ron gave me a lot of room to explore this direction, even though it wasn't a focus of his lab. It was still early days for the field of lipid droplet cell biology, and to me every question I could think of seemed like an open question. How do lipid droplets form? How do proteins localize to droplets and how are they degraded? And what are the functions of lipid droplets and their role in disease

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James with his lab at a holiday party last December.

pathogenesis? It has been very fulfilling to see the field grow over the last 10–15 years, and I feel fortunate to be a part of a terrific community of researchers interested in lipid droplets from different perspectives – from the disease and physiology perspective, the biochemistry and biophysics perspective, and the cell biology perspective.

How important has applying or developing new technology been for your discoveries?

Extremely important! Something I really love is how the questions we have in biology push the development of new technologies and, vice versa, how advances in technology open up the types of questions we can think of answering in biology. Since starting our lab, we've adapted proximity-labelling proteomics, which has helped us develop a method to define high-confidence lipid droplet proteomes and study their dynamics. We've also embraced CRISPR-Cas9 genetic screens, and it's amazing to have the ability to do genetics in human cells on such a large scale. This has opened up a lot of opportunities for discovery, as in every field of cell biology, but certainly for our questions; for example, it led us to the discovery of an oxidoreductase called FSP1, which reduces non-mitochondrial coenzyme Q (CoQ) to generate a local pool of lipophilic antioxidants that prevents the propagation of lipid peroxides and ferroptosis.

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Beyond the topics you work on, what other areas excite you in lipid biology where you think we'll see further breakthroughs in the coming years?

I'm really excited about the recent applications of chemical biology approaches to develop new methods for visualizing lipids and measuring the activity of lipid metabolic enzymes; these have huge potential and I think we're just at the tip of the iceberg. Another area that continues to fascinate me are organelle contacts; there's been so

much progress in understanding the tethers that are present at contact sites, and the discovery of new lipid transfer proteins and new modes of lipid transfer, as well as what appears to be local lipid metabolic networks that are operating at these contact sites is also very exciting. Other exciting areas include the further development of methods that allow us to quantify and manipulate lipids, such as lipidomics, fluorescence sensors and engineered enzymes.

Your lab is committed to promoting diversity, equity and inclusivity (DEI) in science, and you've written an essay on the topic emphasizing that the responsibility belongs to all of us. Do you have any words of advice or encouragement to those who have just started to acknowledge DEI issues and are eager to help push for change?

Some things we can all do is acknowledge the problem of exclusion, listen to a wide range of voices in our field, seek to educate ourselves about diversity, equity, inclusion and belonging, and participate in ongoing efforts as much as we can. I think that some of my advice would be to get involved, even if it's something small. This could be through your university if there is a DEI office that organizes education seminars or outreach activities, or through scientific societies such as ASCB and ASBMB that organize events throughout the year and at their annual conferences. There is still a ton of work to do and we really need the entire research community to be committed, and to prioritize and value these efforts in order to move the needle on DEI issues. [To see James's essay, please visit <https://www.molbiolcell.org/doi/10.1091/mbc.E20-09-0575>.]

Why did you accept the invitation to become a Guest Editor for Journal of Cell Science?

When Michael Way, the Editor-in-Chief of Journal of Cell Science, contacted me, he made a pretty compelling case that there's been a lot of recent technological and conceptual advances that have led to exciting discoveries in lipid cell biology, and that perhaps the cell biology of lipids may not have been sufficiently appreciated in the past, despite being so interesting and important. This resonated with me and I saw a special issue around lipid biology as a great way to highlight all the exciting work that's going on in the field, and attract lipid biologists to Journal of Cell Science as a terrific home for their research.

Could you describe what your role was as a Guest Editor, and what you experienced to be the most challenging aspect?

I received all submissions of lipid cell biology-related research articles, and then secured referees in the field to review these articles. I then helped by being a 'mediator' between the reviewers and the authors to ensure a fair and timely review process, which hopefully was a good experience for all, and achieved our common goal of publishing rigorous and exciting science. We all hear about horror story review processes, where reviewers ask for the universe; so, I think as an editor or mediator, it's important to temper such reviews and focus them on the critical issues that ensure that the conclusions the authors have presented are sufficiently supported, within the scope of their manuscript. In my Guest Editor role, I also came to appreciate the breadth of the lipid cell biology field even more. It's incredibly diverse and I think we really see this reflected in the scope of the research in this special issue – ranging from the development of new lipid probes to advances in our understanding of lipids in the aetiology of various diseases to mechanistic insights into how lipids are stored and used in cells for energy, signalling and the regulation of proteins. This kind of depth to this area of biology is one of the things that made my job challenging, but also fun. I think the most

challenging part was to make sure that I secured reviewers in a timely fashion, because we always hope to make the review process as fast as possible for the authors – and this is something I also always appreciate when I'm on the submission side.

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When you're not doing research and are not a Guest Editor, what are the things you do in your free time?

We have two children, a two-and-a-half-year-old daughter and a 3-month-old son, so right now work and family pretty much takes

up all my time. Hopefully, we'll be able to begin travelling again, as I really miss travelling with my family, as well as travelling for conferences and having the in-person interactions with colleagues and friends from around the world.

I've also heard that you practiced kung fu in the past...

I haven't been practicing kung fu as much recently because of work and family responsibilities, but I hope this is something I can get back into once things calm down a little bit. Growing up, I did different styles of martial arts and then got interested in a style of kung fu called Hung Gar in college. When I was a postdoc at Stanford, I ran a kung fu club, and I gained a lot of great friends and experiences through my training – so it's always been a lot of fun and I think it is important to have a creative outlet.

James Olzmann was interviewed by Máté Pálffy, Features & Reviews Editor at Journal of Cell Science. This piece has been edited and condensed with approval from the interviewee.