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PEOPLE & IDEAS

Ori Avinoam: Mind, body, and membranes in shape

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Ori Avinoam studies membrane remodeling with a focus on cell-to-cell fusion through the lens of correlative light and electron microscopy.

As far as he can remember, Ori Avinoam has been searching for explanations for how things and people "work." A native of Haifa, Israel, Ori has always been curious about human reactions, emotions, and behavior to such an extent that he still considers becoming a psychiatrist "when he grows up." But his curiosity for fundamental cellular mechanisms in living organisms was even greater than his obsession with the human mind. After completing his military service, which is mandatory for all Israeli citizens, Ori backpacked through South America for seven months—this experience left a big impression on him. "On a philosophical level, I realized biology was the lens I wanted to see the world through." So, once back home, he enrolled in a bachelor of science in biochemistry, but it wasn't until the end of his undergraduate studies, while being an intern in Benjamin (Beni) Podbilewicz's lab at the Technion-Israel Institute of Technology, that he became fully aware of what science was about: "Not only was science about answering questions or speculating wildly, but also about developing a sense for serendipity and embracing memorable moments, like looking through the microscope, when you might be the first and only person on Earth that has seen the natural world from this particular perspective... and then, the burning need to share it just follows."

Ori remained in Beni's lab for his PhD in cell and developmental biology, where he focused on eukaryotic fusogens in viral and developmental cell fusion—he also spent some time training in the lab of Judy M. White at the University of Virginia, whom they collaborated with. Ori then moved to Europe for a postdoc in the labs of Marko Kaksonen and John Briggs at the European Molecular Biology Laboratory (EMBL). That was in 2012, shortly after Marko and John developed a technique to combine fluorescence and electron microscopy to image the localization of subcellular structures with high spatial precision, of the order of 100 nm. Although Ori missed the "birth" of correlative light and electron microscopy (CLEM), his key contributions made this technique flourish during its "toddler" years. He applied CLEM to reawaken one of the most debatable questions in the endocytosis field, which is how the curvature in clathrin-coated pits is generated. Ori returned to Israel in 2017 to establish his own lab at the Weizmann Institute of Science, where he combines genetics, biochemistry, and microscopy to understand membrane remodeling during myoblast fusion in vertebrates.

Ori has recently been selected as a European Molecular Biology Organization Young Investigator (2021) and awarded with a Proof-of-Concept grant from the European Research Council (ERC; 2022) to exploit the commercial potential of his ERC-funded project on myoblast fusion. We asked Ori about his scientific journey and future research plans.

Ori Avinoam. Photo by Ohad Herches.

You have been working on membrane fusion in different biological settings your whole career; what interested you about membrane remodeling?

My interest in membranes started from Prof. Dani Cassel's cell biology classes. The ingenious approaches taken and questions asked by George Palade and Günter Blobel on the fundamentals of cellular organization and membrane protein trafficking captivated me, so I looked for a research internship in a biochemistry lab to work on membrane proteins. I interviewed with Beni Podbilewicz, even though his lab was working with *C. elegans* and seemed quite far from my interests. At the door, right after my interview finished, Dr. Gidi Shemer—then a postdoc in Beni's lab and now a faculty advisor at University of North Carolina at Chapel Hill—asked me if I wanted to see some worms... Watching a worm crawling in a lawn of bacteria was peaceful, but when Gidi pulled the lever and switched the view from brightfield to fluorescence my heart skipped a beat—what was a worm a second ago was now an

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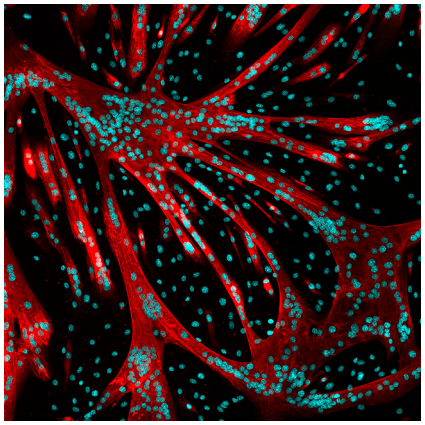

Differentiated murine myoblasts in vitro. Nuclei (cyan) and Myosin Heavy Chain (red) staining shows the characteristic multinucleated myotubes. Image courtesy of the Avinoam lab.

organized collection of bright nuclei moving in space. That was when I fell in love with microscopy and started working on membrane remodeling, specifically on cell-to-cell fusion in the context of *C. elegans* development and tissue morphogenesis. I turned to virology tools because the proteins mediating fusion between the viral envelope and cellular membranes were relatively well characterized, and I wanted to understand how a family of eukaryotic fusogens (AFF-1, EFF-1, or collectively FF proteins) could mediate worm cell fusion (1). By the end of my PhD, I was frustrated by how difficult it was to decipher the underlying mechanisms of cell fusion without seeing the proteins and the membrane together at high resolution. I approached Marko Kaksonen and John Briggs for a postdoc after reading a paper by Wanda Kukulski in *JCB*, where she showed it was possible to correlate fluorescence and EM information with very high precision (2). CLEM seemed to provide the means I was looking for—it increases the interpretability and throughput of EM data acquisition, allowing a meaningful quantitative analysis of multiple events at multiple different stages and the ability to understand the structural phenotypes associated with the presence or absence of components.

When I started my own group, I wanted to apply biochemistry, microscopy, and genetics to understand myoblast fusion in vertebrates as another paradigm of cell fusion. However, I quickly realized that skeletal muscles are complex cells that have a highly spatialized membrane system that must be maintained in the face of contraction, injury, and cell fusion throughout life—fusion must be tightly regulated during muscle regeneration to avoid the disastrous consequences of premature fusion of myoblasts to actively contracting fibers. Moreover, plasma membrane and organellar homeostasis need to be reestablished after every fusion event. There were suddenly many more layers of complexity, and we had to start synthesizing insights across huge scales—going from the events and machineries that assemble on the membrane to mediate fusion, to the reorganization of the entire cell pre- and post-fusion.

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

My lab has expanded to other areas where membrane remodeling plays a physiological function. We use a variety of cell culture and in vivo models, including worms, flies, and mice, which offer the unique opportunity to understand how membrane remodeling processes adapt to maintain cell and tissue homeostasis against fluctuating demands. For example, many exocrine secretory glands utilize very large vesicles, with diameters reaching up to 10 µm, roughly the size of a yeast cell. The membrane surface area and internal volume of these vesicles are orders of magnitude greater than those of conventional vesicles. This increase in size poses formidable challenges to the mechanisms that mediate vesicle biogenesis, trafficking, fusion, content release, and homeostasis of the limited apical surface. We want to answer how these challenges are addressed at the molecular level at each vesicle and at the level of the entire secretory tissue. We have made some progress toward unveiling the molecular regulation of some of these challenges—we recently reported that actomyosin-mediated crumpling of large vesicles in exocrine cells prevents them from expanding and diluting the apical surface, which allows for efficient content release while keeping the plasma membrane homeostasis during extended periods of secretion (3)—[but] there is still work to do.

What kind of approach do you bring to your work?

My approach is people oriented. I'm the scientific manager of the lab, but I also guide people and cultivate scientists by providing an environment that allows everyone to maximize their potential. I encourage an environment of questioning, of self-awareness, of mindfulness—I practice and teach yoga, so that may help [smiles]. I am passionate about what we do, and I try to be as authentic and transparent as possible—what you see is what you get, the good days and the bad. I strive to create a truly inclusive and diverse team by embracing uniqueness and inspiring people to find out who they are. Come as you are but don't stay the same.

With family—Ori's partner Yuval and twins Lavie and Bar. Photo by Ohad Herches.

What did you learn during your PhD and postdoc that helped prepare you for being a group leader? Is there anything you were unprepared for?

During my PhD, I learned the importance of storytelling, having the freedom to do experiments without thinking about how much stuff cost, and how easy it is to lose sight of the big picture, especially when experiments fail. From the postdoc at EMBL I learned to just go for it—that was the EMBL spirit. We had nearly unrestricted access to every technique and equipment with extremely professional people around, so we were only limited by how much time, motivation, and ideas we had.

Working in a lab meant spending every day with a group of peers roughly interested in the same things I was interested in. That's

very different from heading a lab. I was mostly unprepared for the transition from being a workaholic postdoc to becoming a mentor and a team leader. I didn't have a clear view of the skills I needed to develop to lead a research group.

What have been the biggest accomplishment and the biggest challenge in your career so far?

During my PhD, I played around with bioinformatics and predicted that the proteins mediating cell fusion in *C. elegans* are structural homologs of a specific class of viral surface glycoproteins that mediate virus-to-host cell fusion. If true, this meant that the viral and eukaryotic proteins emerged from a common ancestor, and the idea was very exciting, but at the time the prediction was wildly rejected at meetings and by the reviewers who called it "too speculative" and asked to omit it from the paper. Although I only had a small part to play in showing it experimentally (4), I still consider it my biggest accomplishment and a reminder that it is easier to defend a dogma than to break it. It's also the reason I encourage my team to do experiments behind my back if they do not agree with me.

Coping with the enormous amount of uncertainty and self-doubt has been my biggest and constant challenge, and it dwarfs all others.

It seems that you have overcome the scientific uncertainty at least; your research on myoblast fusion was the foundation for your ERC Proof-of-Concept grant and has been key for establishing a biotech company. Could you tell us a bit of how this journey was?

Serendipitous [laughs]. I never planned to go into translational research. It was the outcome of a basic research project that we were working on in collaboration with Prof. Eldad Tzahor, also of Weizmann. Our institute has a great culture of collaboration between research groups. The idea was very simple. We identified a pathway, conserved in chicken, that can be manipulated to stimulate skeletal muscle formation in vitro (5), which was directly applicable to the field of cultivated meat. The Technology Transfer platform here at Weizmann was very supportive, but there was still a long way to go. We first had to start raising funding and making concrete research plans for proof-of-concept experiments. The ERC Proof-of-Concept grant was ideal because the project was an offshoot from my ERC-funded project on myoblast fusion. Eldad also reached out to FreshStart, a global Foodtech incubator, and they immediately tapped into their support network of industry professionals, who helped us develop our early-stage ideas into maturity. It has been an incredible learning experience and a stimulating thinking space, but basic science remains my focus.

I'm glad to hear that—the scientific community is surely happy that you stay in basic science. What would you change in academia to make it easier for basic scientists?

There is too much competition for resources and funding. It seems that the funding and the number of people in research are out of balance at all levels. We need to invest more and in people instead of detailed research proposals that are often not more than thought exercises.

Any wild scientific idea you would like to explore if you had unlimited funding?

I'd study the effects of gravity on muscle maintenance and regeneration. I think space travel is the next frontier for human exploration, and I'd like to be part of it.

Maybe we'll see your lab on the front page of the newspapers for your research on this topic soon, but until then, and until we can travel back in time, let's do an imaginary exercise. If you could rewind to day 1 of you being a principal investigator, what would you change?

Day 1 on the dream job always looks like a dream; at 6 months you wake up and realize that every three steps forward were followed by two steps back. If I went back now, I'd take it one step at a time to get to the exact same place with much less work and worry—probably one of the best [pieces of] advice I've ever been given would apply here: "Take it easy and don't take yourself too seriously." My learning curve involved a million mistakes, and I am still learning.

Putting now your scientific path in perspective, any tips for a successful research career?

Make sure you ask questions you really want to know the answers to—a burning desire to know seems crucial while a burning desire to succeed seems dangerous.

To finish this interview on a more personal note, what has been your biggest accomplishment outside of the lab?

Starting a family—since both my partner and I are male, we had to overcome multiple challenges to start a family. It took two and a half years from taking the first step to the birth of our twins through surrogacy, and I couldn't be happier about our journey into parenthood.

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