

PEOPLE & IDEAS

Ruth Scherz-Shouval: Together we can ask big questions

Lucie Van Emmenis 

Ruth Scherz-Shouval is an Assistant Professor in the Department of Biomolecular Sciences at the Weizmann Institute of Science, Israel. Her lab is interested in the tumor microenvironment, how stress responses can shape the tumor microenvironment, and also how different cells within the tumor microenvironment interact. We talked about how her interest in science began at an early age, the impact of having strong female role models, and ways to encourage collaboration and create an engaging and welcoming lab environment.

Tell us a bit about your background and how you first became interested in science.

I was born in Jerusalem, Israel, and grew up in Israel and in the US. I grew up as a "nature child," hiking Mount Rainier in the US and the Judean Desert in Israel.

My love for hiking and nature sparked my interest in science—I wanted to understand how things work. Both my parents are scientists, and growing up, no fact was ever taken for granted. I was encouraged to question how the world works, how clouds bring down rain, whether God is real, and what drives the differences between boys and girls—everything was open and everything could be a topic for discussion. I would never take no for an answer without a detailed explanation. I was always allowed to be curious, and I learned not only how to ask questions, but also that asking questions is a very important part of life.

Did you always want to be a scientist?

I think I always knew that I wanted to be a scientist. Being a nature child, I thought I would be a marine biologist or cave explorer—something that is more about being outdoors. But when I took biology in high school and got exposed to molecular biology, I realized that that's much more interesting! I am still interested in very big questions, but I want to understand the

mechanistic details that underlie these large processes.

How did your career in science begin, and how did you get to where you are now?

I started as an undergraduate at the Hebrew University in Jerusalem, and then I moved to the Weizmann Institute for my MSc, which turned into a direct PhD in the lab of Zevi Elazar, a generous mentor and extremely creative scientist. I was eager to move to the next step in the path to an academic career: a postdoc fellowship abroad. At this point, I was already married and the mother of two daughters. My husband was pursuing his own career as a physician, and our timelines were not aligned. Together, we decided it would be better to stay in Israel until he finished his residency, and only then go abroad. While waiting for him to finish his residency, I did a first short postdoc. I remember when I first talked to my postdoc mentor, Moshe Oren, a world-renowned cancer researcher, I told him that even though I was only going to be in the lab for two years, I wanted those two years to be meaningful and productive. He smiled, in what I later learned was his way of saying "I expect nothing less." Indeed, I had a terrific project, and I was able to publish during this time, so rather than becoming a gap in my career, this period was a successful milestone. Later, my husband waited for me



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for two years to finish my second postdoc and supplemented his clinical fellowship with vast research experience and a high-impact publication. I think that the mutual respect we have for each other's careers, and the understanding that together we can make it work for both of us, is an important lesson in combining family and science.

In 2010 we moved to Boston, where I did my postdoc at the Whitehead Institute, MIT, with the late Susan Lindquist. Susan was a stellar scientist, an amazing mentor, and an advocate and role model for women in science. Sadly, she passed away a year after I finished my postdoc. Susan shaped the way I

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see and do science. She taught me how to be a mentor and how to find and ask the big questions. She was very bold, and taught me that you have to go out there and take what you can and not just wait for things to happen to you. She gave me the courage to pursue my goals. And she was a mother herself. I had my third child towards the end of my postdoc—he was born with my big postdoc paper—and shortly after, we moved back to Israel, I joined the Weizmann, and I've been here ever since.

Your lab's research focus is on the tumor microenvironment. When did you first become interested in this specific area?

My scientific passion has always been evolution, and understanding how organisms, tissues, cells, and proteins survive through changing environments. Very early on, I got interested in the interplay between stress and evolution. My earliest discovery, as a BSc student, was a mechanism for stress-induced formation of multi-cellular stalk-like structures in yeast. Intrigued by this dramatic adaptation, I went on, as a PhD student, to investigate autophagy. I found that a key autophagic protease is redox regulated, an insight that led me to study the role of redox in regulation of protein activity. These studies led me to realize that stress responses are extremely important in shaping pathology. Eager to understand how such processes promote cancer, this was the focus of my postdoctoral studies. I first studied stress responses in the context of the cancer cells themselves. Specifically, I studied the role of p53 in regulation of autophagy and discovered that, despite its tumor-suppressive role, p53 may be subverted in cancer cells to increase their survival through regulation of autophagy. Very quickly, I realized that environmental stresses, like starvation or oxidative stress or prototoxic stress, don't just happen to the cancer cells; these conditions affect the whole tumor. At that point in time, it became clear that tumors should be viewed as more than just cancer cells, and the vascular and immune microenvironment were gaining a lot of attention. The stromal microenvironment, i.e., cancer-associated fibroblasts (CAFs), were much less studied, and I was curious to understand how stress responses affect the protumorigenic behavior of these cells. I was fascinated by these changes that could not be explained by mutations; when a mutation

occurs, the cancer cell changes in a non-reversible way. It makes sense that this would lead to a pathological outcome. But cells in the tumor microenvironment are relatively genomically stable, and the changes are not driven by mutations. This also makes the cells of tumor microenvironment very plastic and amenable to manipulations. In my postdoc, I focused on the proteotoxic stress response and discovered that the transcriptional regulator of this response is activated in CAFs and shapes their protumorigenic identity. I found this intriguing and complicated and of great therapeutic potential, and when I opened my lab at the Weizmann Institute in 2015, I set to elucidate the mechanisms by which tumors reprogram their local environments, and the crosstalk between cancer cells and the stroma.

I like that you've been able to take aspects from your PhD and postdoc work and bring them together to be the focus of your lab now. What are you working on in the lab at the moment, and what are you excited about?

I think in the first few years of the lab, and also where the field has been in the last five to six years, it was more about classification and characterization, and understanding which subpopulations of fibroblasts exist. It took a while for single-cell RNA sequencing and fibroblasts to finally meet, longer than for cancer cells or immune cells, and so we were very busy with just understanding what kind of subtypes we have. Now we finally have enough information and tools to start understanding the "microenvironmental habitats" that comprise different tumor microenvironments. For example, how and why is a BRCA-mutated breast tumor different from a BRCA wild-type breast tumor, or how is BRCA-mutated breast cancer similar to BRCA-mutated pancreatic cancer? I think that there are two major forces shaping the tumor microenvironment: mutation dependencies and organ dependencies. We have several projects that aim to define the relative contribution of organ and mutation dependencies to the tumor microenvironment. As I already alluded to, we're looking at BRCA-mutated cancers. We have previously studied the effects of BRCA mutations on the CAF composition, and we found that the compositions are different between BRCA wild-type and mutated breast cancers (Friedman et al., 2020). This led us to hypothesize that BRCA mutations in cancer

cells could actively affect CAF compositions, and we tested this hypothesis in another type of BRCA-mutated cancer: pancreatic cancer. Here too, we found different CAF compositions in BRCA-mutated versus wild-type cancers (Shaashua et al., 2022), and we are now exploring the generalizability of this phenomenon and its therapeutic implications.

The other concept that I'm very excited about is viewing CAFs as part of the immune microenvironment. Although CAFs are not immune cells per se, we now know that they are very much immunomodulatory (Arpinati and Scherz-Shouval, 2023). They interact with various immune cell types and are able to modulate their activities in different ways, which we are actively investigating. This concept has far-reaching therapeutic implications, and we are building experimental and computational approaches to study these.

What are some of the qualities that you learned during your graduate studies or postdoc that you maintain and foster in your own lab and your own work?

I learned to have a lot of interaction with my students and talk to them about science, as well as topics around science, to make sure we have an open atmosphere in the lab. Something I learned both from my PhD and my postdoc is to take people who are nice and who will get along with everyone in my lab. When I interview candidates, I always ask them to talk to my students, and I take their opinions very seriously. I also learned not to be shy about asking questions, even if it is a "far out there" question, because those are often the most interesting questions. From my late postdoc mentor, Susan, I got the courage to speak back and stand up for myself.

Another thing that I foster in my lab is to celebrate submissions. We also celebrate when papers get accepted, or when big grants get accepted, but we always celebrate the first submission because at that point we have done everything we could, and from that point it's out of our control. We also celebrate birthdays, and try to have at least three lab trips out in nature every year.

It's so important to celebrate all of the successes of the lab, no matter how small! What's the part of the role that you really enjoy?

Talking to my students! The other thing that I like about being a PI is that there are

multiple different projects all happening at once, so the breadth of what can be done under my control (I would say not full control, maybe half control?!) is much larger; so together, we can ask big questions.

I also really like when someone in my lab comes up with a question I haven't thought of and they are really excited about it. What we recently did—and I've been wanting to do this for a long time—is an opening-of-the-year brainstorming lab meeting! We had three themes: (1) What is a new experimental system that you would like to work with? (2) What is the most exciting question you can think about? (3) What is a really cool technology that you would like to bring to the lab? It didn't have to be their own project; it could be a project for an imaginary student (because often if you think that you actually have to do something, it almost gets more scary!). We came up with multiple exciting ideas, which we then followed up on by getting into groups and coming up with several doable projects from all of the ideas we had thought of. We're actually now moving forward with two of the projects that we came up with!

One other thing that we recently did is feedback meetings—we talked about project goals and career goals, and mutual expectations. I really enjoyed the process, and I think that my lab did too.

The ability of a PI to create a safe place for collaboration and feedback is so

important, and it sounds like this is a really effective way of doing it! This year at JEM we are focusing on women in STEM and using the People & Ideas series as a way to discuss topics that are important and relevant to women in STEM. We have already heard about the importance of mentorship and the need for parity at all levels of science; is there a specific aspect of scientific culture that you feel requires change, or an area that you feel passionately about?

I do a lot of mentoring, not only of my own students, but for female PhD students. I feel that having role models who will honestly discuss challenges and opportunities is really important. I think despite all the progress, there is still unconscious bias. People already think that they're doing a lot, and so that's really where the unconscious part is the hardest. As an example, a very good friend of mine told me that when he gets asked to go to meetings or take part in committees that take place in the evening, he always says that he can't because he needs to be with his kids, and people simply accept that. As a woman, I would never dare say something like that. I wouldn't feel comfortable using my kids as an excuse to not attend a meeting; instead, I would just say I can't attend. So while a lot of things have certainly improved, this is something that is

still challenging, especially when circumstances are harder; for example, during COVID, when parents and especially mothers with young kids were faced with an unproportional challenge. My husband and I share responsibilities equally; he is super supportive, but he's a clinician and during COVID we had to work very creatively and hard to manage everything. I think that things are getting better, but when things get harder, they are still much, much harder for women.

And finally, while not in the lab, how do you like to spend your time?

Family and sports! I am a swimmer, and swimming is my meditation time. I also like yoga, and I love hiking—it's our favorite family activity, along with camping. I love spending time with my family, with my husband and my kids. Having a family almost keeps me more efficient; the more balls you have to juggle, the more you can fit into one day!

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