

Yaron Fuchs: Exploring the mysterious mixture of life and death

Marie Anne O'Donnell

Fuchs studies how cell death controls stem cell-driven processes.

With a rocket scientist father and a mother who taught, science was regarded as somewhat holy in Yaron Fuchs' family. Traveling between Israel and California during his childhood gave Fuchs plenty of opportunity to explore local insects, lizards, and other organisms and to try and understand their biology and evolution. As a young diving instructor, Fuchs fell in love with the ocean. He "found the coral reef of the red sea mesmerizing and marveled at the complexity and interactions between different species," which laid the foundation for becoming a biologist.

As an undergraduate at Haifa University, Fuchs kept changing his mind about what field of biology he would specialize in. Knowing Fuchs' love for genetics and the marine ecosystem, his mentor, Rachel Ben-Shlomo, arranged an undergraduate research project at the Israel Oceanographic and Limnological Research institute, co-supervised with Baruch Rinkevich. Working on the population genetics of the soft coral *Heteroxenia fuscescens* was a turning point, revealing the thrill of research to Fuchs as he discovered that this coral reproduces solely in a sexual fashion (1).

Fuchs then joined Dina Ron's group at the Technion Israel Institute of Technology in Haifa for his postgraduate studies. At that time, gene silencing was considered relatively difficult and mastering this technique in Ron's laboratory turned out to be a critical point in Fuchs' career, enabling him to reveal that a gene termed *Seif* was a crucial feedback antagonist of NF κ B and proinflammatory cytokines (2). In addition to inflammation, these signaling molecules regulate cell death. Fuchs joined Hermann Steller's laboratory at the Rockefeller University in New York to investigate how apoptosis affects stem cell biology. In collaboration with Elaine Fuchs, Yaron Fuchs discovered that Sept4/ARTS and its target x-linked IAP (XIAP) regulate cell death in hair follicle stem cells and that their apoptosis is profoundly important for regulating the hair follicle stem cell proliferation and tissue regeneration required for wound healing (3). Fuchs then returned to

the Technion to establish his own group and continue charting the unexplored waters of how apoptosis controls stem cell biology and tissue regeneration. We contacted him to find out more.

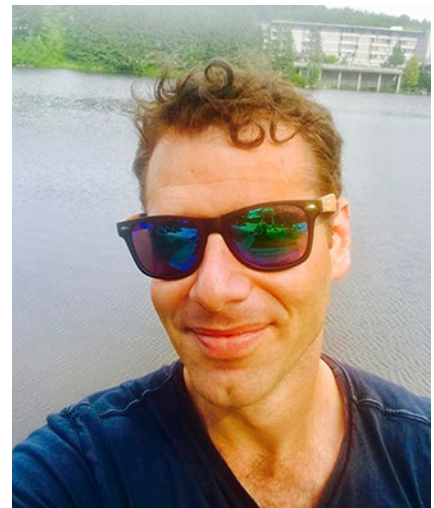
What first drew you to study stem cell apoptosis?

For many years, the stem cell field focused on investigating self-renewal and differentiation, leaving the mechanisms for stem cell elimination relatively untouched. I found it quite remarkable that even though stem cells are featured heavily in the scientific spotlight as key drivers of tumorigenesis, and resistance to cell death is considered a hallmark of cancer, incredibly little is known about the specific mechanisms used for eliminating stem cells.

"Don't overlook bizarre results. The most fascinating projects can emerge when you least expect them."

What is your laboratory actively working on?

My laboratory has branched into several different directions of research. We seek to understand how stem cells use the apoptotic machinery for their elimination and the effect this has on different aspects of stem cell biology and stem cell-dependent processes. We have established a comprehensive in vivo system that enables us to investigate the function and regulation of key apoptotic proteins in distinct stem cell populations. By combining advanced multi-color lineage tracing with intravital imaging, we examine how the manipulation of apoptotic pathways affects not only stem cells but also their progeny during regeneration and tumor development. We recently started to explore how the apoptotic machinery can be harnessed for various functions outside the realm of cell death (4). Intriguingly, we find that "apoptotic" proteins regulate cell proliferation, organ size, and tissue regeneration independently of their function in



Yaron Fuchs. PHOTO © YARON FUCHS.

apoptosis. In addition, we seek to uncover novel stem cell populations and elucidate the role they play in tissue homeostasis, tissue repair, and tumor formation. We recently established novel organoid platforms and use them as models for understanding the behavior and contribution of different stem cells. I hope that our research may be translated into novel stem cell and apoptosis-based approaches for regenerative medicine and tumor therapy. But in general, I'd just like to continue this incredibly exciting journey.

What kind of approach do you bring to your work?

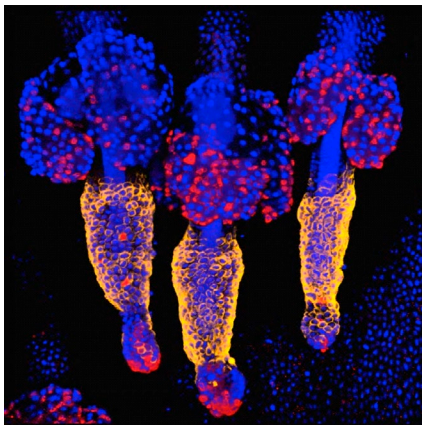
I'm an optimist, through and through. I try to motivate my students to look at things in a positive way even if experiments don't work as anticipated. There is no failure, everything is a result and everything is feedback and you may learn significantly more from experiments that you deem "unsuccessful."

What did you learn during your PhD and postdoc that helped prepare you for being a group leader?

I owe a lot to Dina Ron, who taught me how to ask a scientific question, how to control and organize an experiment, and, most importantly, how to be strong and believe in myself. From Herman Steller, I learned how to think big, how to choose the right people for my laboratory, what generosity is, and

modonnell@rockefeller.edu

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The hair follicle stem cell niche (orange). IMAGE © YARON FUCHS.

how to see the very best in people. I wasn't prepared for being away from the bench and if there is one thing I miss most, it is the feeling I had right before finding out whether or not my experiments worked. My heart used to race and I was filled with hope and anticipation. Now I see the results of my students' experiments but, as incredible as they might be, I miss that feeling.

What has been the biggest accomplishment of your career so far?

I have been privileged to train phenomenal students and fellows from all over the world. I would say that helping shape this new generation of scientists is my biggest accomplishment. I try to instill in them the belief that they can make groundbreaking discoveries and go the scientific distance. I feel that they are all part of my extended family and watching them excel makes me incredibly proud knowing I have played a small part in their success.

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

Both my wife and I are very passionate about our careers and trying to balance this with raising our son has been quite a challenge. Thankfully, we both come from families with scientific backgrounds and they understand our dedication and drive. The support we get from our families and specifically the grandparents is priceless.

Who were your key influences early in your career?

During my PhD, the groundbreaking work of Elaine Fuchs, Fiona Watt, and George

Cotsarelis in the field of epidermal stem cells had a major influence on me. I found it intriguing that distinct stem cell populations of the skin can shift their fate and assist in tissue repair. Toward the end of my studies, I came across the innovative research performed by Gines Morata and Hermann Steller. Their groups showed in parallel that, in contrast to the perception of apoptosis as a silent process for the removal of cells, apoptotic cells secrete mitogenic factors that have a dramatic effect on their cellular environment (5). By a process termed apoptosis-induced proliferation (AiP), dying cells instruct neighboring cells to divide, which fuels tissue regeneration. Many of the treatment strategies we currently use to try and eliminate cancer cells were designed to induce apoptosis; however, the discovery of AiP suggests that this approach may be counterproductive. This got me thinking: How do "immortal" stem cells undergo apoptosis? Does the AiP mechanism affect stem cell behavior? To what extent does apoptosis affect stem cell-dependent tumor formation and tissue regeneration?

"Don't miss opportunities to be silent; you learn most when you just listen."

What is the best advice you have been given?

First, choose the right research question. Before you start any project try to imagine how the project could unfold. Ask yourself, "If everything works the way I expect, how important will this finding be?" From that you'll know the potential of this research avenue, how pioneering it is, and if it's worth exploring. Second, don't overlook bizarre results. The most fascinating projects can emerge when you least expect them.

What hobbies do you have?

I've been practicing the art of Tae Kwon Do for many years now. The beauty of it is that while I train, nothing else exists, my mind is clear, and I'm completely submerged in the experience. I try to incorporate the five tenets—courtesy, integrity, perseverance, self-control, and indomitable spirit—into everything I do and particularly my science. I also love diving, trekking, and riding motorcycles.

What do you think you would be if you were not a scientist?

I briefly ask myself this question every now and then. Honestly, I was never able never to come up with an alternative.

What has been your biggest accomplishment outside of the laboratory?

My family. I have an incredible wife whom I met during my PhD and without a doubt her support is what enables me to keep going. Her PI originally gave her my phone number in order to establish RNAi in his laboratory and we moved in together at the end of our first date. I'm fairly sure she would agree that by far our most successful experiment is our son, Tzuk.

Any tips for a successful research career?

Work hard. Believe in yourself and in your findings. Be critical but fair. Lead by example and try to understand what every person in your team needs in order to flourish. Don't miss opportunities to be silent; you learn most when you just listen. Be provocative and think outside the box. Exercise several times a week; it's the best mental cure I know. Smile to the world and you'll find that the world will smile right back. Don't forget that this is what you decided to dedicate your life to, so try to be your very best and enjoy every moment!

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The Fuchs family: Inbal, Tzuk, and Yaron. PHOTO COURTESY OF YARON FUCHS.