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PEOPLE & IDEAS

Eran Elinav: Beyond the microbiome

Stephanie Houston

Eran is the head of the microbiome-focused research group at the Weizmann Institute in Israel. He has published seminal work demonstrating the importance of the microbiota in many different systems, from post-dieting weight gain to circadian rhythms. Recent work from Eran and colleagues shows how probiotics perturb rather than aid the recovery of the microbiota following antibiotic treatment in humans. We contacted Eran to find out about his journey in science so far.

Where did you grow up?

I grew up in the southern Israeli city of Beer-Sheva, situated in the midst of the Negev desert. I remember it being a very happy childhood, filled with a sense of freedom and frequent encounters with the wild desert that surrounded me. I knew very little of the outside world; even a visit to the "big city" of Tel Aviv seemed like a daring adventure. After completing elementary school, my family relocated to New York City due to my father's job position, which was a tremendous culture shock for me. I started high school in the Manhattan Lennox high school, not speaking a single word of English, knowing anyone, or being familiar with NYC '80's culture. But my quick acclimation into this new setting taught me an important lesson that I carry with me until this day: willpower, perseverance, and belief in myself could help me overcome even the most extreme of challenges. My NYC high school days ended up being a period of intense learning and self-development and a nurturing encounter with the world. Following my high school graduation, I returned home to serve (like any 18 year old) in the Israeli army, as a naval submariner (final rank of captain) for over 4 years. This was another significant period of development of leadership skills, comradery with my best friends until this day, and, most importantly, the development of intuitive troubleshooting skills, with an ever-lasting confidence that everything is solvable and doable.

When did your interest in science begin? What was your first experience with science?

My interest in science developed during high school, where I first discovered the complexity and wonder of the human body. I became intrigued and curious in its components and how they come together to fulfill so many tasks in forming who we are. The same curiosity led me to medical school, and later on to my basic science studies and career.

Where and with whom have you studied (undergraduate, graduate, postdoc)?

Following my discharge from the Israeli navy, I studied medicine at the Hebrew University in Jerusalem. I then enrolled in a clinical career that included an all-round internship and a residency at the Hadassah-Hebrew University Medical Center. I then trained as a resident at the Hadassah Medical Center Gastroenterology Institute but developed a passion to perform basic science, leading me to relocate after a year to serve as a senior physician-scientist at the Tel Aviv Medical Center Institute for Gastroenterology and Liver Disease while performing, in parallel, my graduate studies in basic immunology at the Weizmann Institute of Science in the laboratory of Professor Zelig Eshhar, who is well known for the development of CAR-T (chimeric antibody receptor T cell) treatment for cancer. During my graduate studies, I developed CAR-T regulatory cells that feature predetermined specificity toward inflammatory bowel disease–associated antigens as a means of treating autoinflammation. The CAR-T reg modality, based on my work with Zelig, is now being tested for human use. In 2009, I relocated to Yale University, where I performed a postdoc with Professor Richard Flavell, focusing on the then new and exciting links between the gut microbiome and innate immunity. There, we characterized the NLRP6 inflammasome and demonstrated that it played a role in regulating host–microbiome interactions and in ensuing risks of developing colitis, cardiometabolic syndrome, and colorectal cancer. In 2012, I was recruited to the Weizmann Institute of Science to establish the first microbiome-focused research group in the institute (and in the country).

Eran Elinav

What interested you about your current area of study?

The microbiome fascinates me, as it represents a complete change in paradigm from anything that I've learned about in medicine and in science. In a period of only around a decade, we've learned to realize that our body is composed not only of eukaryotic human cells, but also of roughly equal numbers of microorganismal cells, which carry millions of genes and feature functions that are essential for the healthy functioning of the "human machine." We've also learned to appreciate how little we know about the molecular "alphabet" dic-

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Elinav group—winter holiday party, December 2017.

tating the cross-talk between our human and microbial parts, but realized that by understanding these complex communication channels, we will slowly be able to better understand the pathogenesis of complex and common "multi-factorial" disease and identify new therapeutic targets for them. This adventure, involving two of my biggest loves, medicine and science, focuses on search and discovery for unknown parts of biology. This is fascinating to me, and hopefully to my students and postdocs, as it incorporates a deep dive into the very basic principles of life while potentially having very actionable implications on the health of millions of humans.

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

Our laboratory has now grown to include over 30 students, postdocs, and technicians from all over the world. We study many aspects of host–microbiome interactions and their potential involvement in human disease processes (Levy et al., 2015; Zeevi et al., 2015; Thaiss et al., 2016, 2018; Suez et al., 2018; Zmora et al., 2018). Our interests are now expanded beyond the gut microbiome, and we are looking into other microbial niches in the mammalian body: the skin, respiratory tract, and urogenital track. In each, we find a microbiome that differs in its biomass, composition, and function but is uniquely fit to the niche it occupies. Each of these microbiomes contributes to vital functions that are unique to their organ and its precise functions, and in each of these ecosystems, altered communications with the host lead to a propensity of developing disease. We thus are now looking into microbiome involvement in a variety of human disorders ranging from infection, auto-immunity, metabolism, and cancer to even neuro-degeneration.

What kind of approach do you bring to your work?

There are several principles that are important to me in my work. The first is to endorse new ideas that often come from the students and postdocs, and not necessarily only from me. As such, several of the solutions that our laboratory has come up with, to some of our biggest challenges, came from young and seemingly inexperienced members of the group. It is therefore very important to me that I establish an atmosphere in which everyone, regardless of their "status," can contribute to the scientific process.

A second principle, equally important to me, is to try and comply with the highest scientific standards in our work. It is of course obvious and critically important that we share and adhere to our principles of good practice, including documentation, repetition of experiments, and implementation of the highest possible professional and ethical standards. However, as we work very hard, we are bound to make some mistakes along the way; we are only human. It is therefore of personal importance to me that we acknowledge this as part of our work process and all feel free and obligated to report our mistakes when they occur. In the spirit of the famous Israeli air force self-reporting tradition, all of the group members (including myself) are encouraged to share their mistakes and pitfalls, which never result in punishment or scorning but rather in a constructive discussion aimed at minimizing these errors in the future. We are never mad about mistakes, only about lack of their reporting.

Finally, it is important to establish a collaborative and friendly spirit in the laboratory. We have a fantastic group of people coming from many different disciplines where they are considered to be bright prospects. Teaching them to work together, collaborate, and join forces in tackling big questions is one of my major missions in the laboratory, and I strongly believe that only through collaborative efforts can complex problems in biology can be adequately answered. Moreover, we spend so much time in the laboratory doing science that having a friendly and fun atmosphere is a critical component, so we try to complement our hard scientific work with a family atmosphere and joint activities such as trips, meals, and parties. I am hopeful and certain that members of our laboratory take this positive attitude into the next steps of their career as independent researchers.

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

My PhD with Zelig Eshhar, who was the first to develop the CAR-T approach, was my first full-time basic research experience. With a small group of students mainly focusing on translational applications of T bodies (at this time, the proof of efficacy of CAR-T cells as a new form of immunotherapy was an exciting field of research), I learned both the fundamentals of scientific work and the challenges of its application into medical practice. I followed with a postdoc at Richard Flavell's laboratory at Yale University. Richard, one of the smartest people I have met, has become a role model for me in running a large group of ambitious and talented postdocs while attending to each of them in a highly person-specific manner and minimizing frictions. Doing so in a highly competitive environment, while constantly tackling and solving problems and pitfalls arising from the many concurrently running projects in his laboratory, was quite amazing to me. And Richard does this all with a good spirit and a fine British sense of humor. Collectively, I felt that my clinical career and graduate and postdoc experiences with different disciplines, people, and cultures have prepared me well for my own independent career phase.

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

Being the first fully devoted microbiome researcher at the Weizmann Institute of Science and in Israel as a whole was a great challenge to me as a young PI. I had to establish multiple research platforms that enabled state-of-the-art research in this new and exciting discipline while it was still only 5 years old. I came to a strategic decision that rather than focusing on my comfort zone, which was at the time the interface between immunology and the microbiome, I would try to establish a complete set of capabilities that would enable us to follow any microbiome lead that would come up in our studies. This resulted in the establishment of automated sample processing platforms, next-generation sequencing and analysis capabilities, culturomics, transcriptomics, an anaerobic facility, and metabolomics platforms coupled with the first germ-free facility in the country, all in par-

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allel. This was a huge task, which was only made possible with endless support from the Weizmann Institute management and personnel, and with the active participation of an amazing group of students, postdocs, and technicians that joined me in this journey. With all due respect to technology, during these "development" years I came to realize that the human asset and contribution are far more strategically meaningful than any instrumentation or pipeline that I would ever develop. Our group, collaborators, and Weizmann personnel engaging in different aspects of our studies is what made us successful.

What is the best advice you have been given?

Listen to your people

The most valuable advice I've been given, which has been personally proven to me, is to listen to my group members. In our group, your formal "rank" means almost nothing to me, and some of the greatest ideas, solutions to problems, and insights came from the youngest of minds. The students are the ones performing the experiments, following the animals and human participants, and tackling the challenges. In those long hours, they are often the ones coming up with the most brilliant ideas and solutions.

Follow the data

In almost every project that we perform, we encounter results that are different, if not opposite, from what we have anticipated, even after multiple repetitions. The first instinct is to blame ourselves, force the results into the framework of our original working hypothesis, or disregard them altogether. Instead, I see it as my obligation to teach my students to follow their data and results, believe in them, and follow up on them. In countless cases, this approach enabled us to finally reach new discoveries and insights that initially seemed counterintuitive.

Report your mistakes and learn from them

One of the great practices I took away from my long military service as an Israeli submarine officer is the habit of reporting of errors. In our scientific work, we constantly make mistakes. A central part of our laboratory culture is that all mistakes are permitted and forgivable, as long as they are fully reported, which allows us to learn from them for the future. Allowing young promising scientists to make mistakes as they develop their "learning curve" in conducting science while teaching them to not shy away from sharing them is essential, in my view, to their development as honest, self-critical future independent scientists.

Be ever thankful

Some advice I keep trying to remind myself of is to be ever thankful of the privilege I was given to be on this career path and do what I love most, which is to explore the unknown. I consider myself very lucky in having the opportunity to contribute to the development of the next generation of scientists. Last, but not least, I am most thankful to my family, who have stood by me through countless years of stress, joy, failure, and success, the endless hours, emotional roller-coasters, and long-standing uncertainty, all of which has had a heavy toll on me and my loved ones, and I am grateful to them for letting me follow my dreams.

What hobbies do you have?

My research and my wife's clinical career as the director of an HIV center at a large tertiary medical center make our family's lives very demanding. Our family hobby, implemented once every 2 years, is to take off with our three children and go trekking at a remote mountainous area, no cell phones included! We've done this since our twins were 1-year-old babies, trekking in the high Nepal Himalayas, Northern Vietnam, Central Africa, South America, and more. This is when we have quality time as a family. We complement these trips with family skiing trips in more conventional mountainsides.

Any tips for a successful research career?

People tend to answer such questions with clichés such as "believe in yourself" and "follow your dreams." These are all true, but I would add the advice of never stay in your comfort zone. Science is a wonderful field, filled with constant failures on the one hand, but near-complete freedom of operation on the other. Many of us naturally tend to stay in our comfort zone, which is associated with much less anxiety and risk. However, I strongly encourage young scientists to dare stepping out of their comfort zones, take their new ideas to unchartered territory, and allow themselves to learn new fields, techniques, and disciplines at any stage of their career. It pays off!

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