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PEOPLE & IDEAS

Iannis Aifantis: An accidental scientist

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Iannis Aifantis is a principal investigator at NYU Langone Medical Center, and his laboratory works on the molecular mechanisms that drive normal stem cell differentiation and malignant transformation. Specifically, they're interested in the genomic, epigenetic, and proteomic regulation of hematopoietic stem cell differentiation and the induction of leukemia and lymphoma; some of their basic research has led to clinical trials in leukemia and myelodysplastic syndromes. I chatted with Iannis to find out about his career in science so far.

Where did you grow up?

I grew up in a small town in the north of Greece, a beautiful and quiet place close to the sea. I couldn't ask for a more "normal" and uneventful upbringing, something that gave me time to focus on things that I loved including literature and music. I was supposed to become a medical doctor, but I "failed" the national exams and "ended up" at the Department of Biology of the University of Crete. I never planned to study biology or be a research scientist, but I was lucky to have impressive professors, most of them fresh out of their postdocs in the US and Europe. It was the early nineties, a key moment in the development of molecular biology and genetics. I became fascinated by gene transcription, immune response, and development, areas that back then appeared to be distinct but have permeated my whole career until today.

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

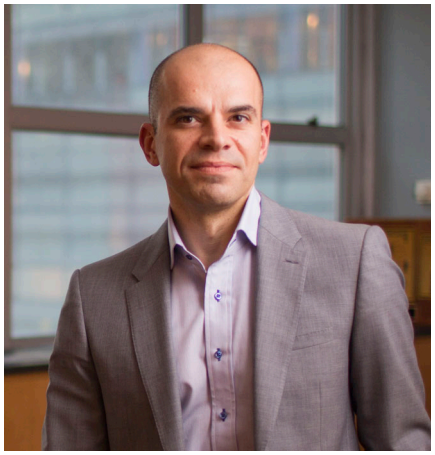
As I mentioned previously, I am an "accidental" scientist; I was never really planning to be a researcher. And there is nothing wrong with that. I was just not lucky to grow up in an environment with enough exposure to science. My first experience in science was as an undergraduate at the University of Crete, fractionating proteins from the lymph of spiders. I know that it sounds unappetizing, but I remember being fascinated by discovering methods of protein purification and studying protein–protein interactions. This is where I learned how to make my own monoclonal antibodies, probing their specificities—something that led me to the study of the immune system.

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

I had the luck to join the laboratory of Harald von Boehmer as a graduate student at the Necker Institute in Paris. These were the early days of lymphocyte development, and the laboratory had just cloned the preT cell receptor. I was involved in some fundamental studies in T cell development, as I was able to prove that this receptor is essential for differentiation of progenitor cells and key "checkpoints" like allelic exclusion or the split between the αβ and γδ T cell subtypes (von Boehmer et al., 1999). After my graduation, I moved with Harald to Boston and the Dana Farber Cancer Institute to do my postdoctoral studies. This was when I started to be interested in earlier studies of T cell differentiation and the signaling pathways (Wnt, Notch, Hedgehog) that cooperate with cytokines and antigen receptors to ensure optimal commitment to the lymphocytic lineage and function.

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

The laboratory is focusing on diverse aspects of induction, maintenance, and treatment of leukemia. We are fascinated by asking novel questions and using the latest cutting-edge technologies to address them. One area that



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is exciting for us is the study of three-dimensional (3D) chromosomal organization in blood cancers (Trimarchi et al., 2014). We recently found that one can differentiate between subtypes of the same disease by simply studying 3D chromosomal landscapes, and that drugs that target specific oncogenic signaling pathways or epigenetic regulation can change 3D architecture and "correct" patterns of enhancer–promoter looping and gene expression. This is an area that has attracted a lot of attention in the last few years and that I believe will teach us more about the way that coding and noncoding areas of DNA interact with each other and control expression. Another novel and exciting area for us is the study of the leukemia microenvironment using cutting-edge imaging and single cell approaches (Tikhonova et al., 2019). It is

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The Aifantis lab, mid-2019, in the lobby of the new NYU Langone Research Building.

interesting that although the notion of tumor microenvironment is so established in solid tumors, it is still in its infancy in leukemia. For me, this body of work enables me to return to my roots and go back to immunology with the study of innate and adaptive responses within the leukemia microenvironment.

What kind of approach do you bring to your work?

I am trying to not be dogmatic, to not adhere to all-encompassing hypotheses, and to let my colleagues in the laboratory develop their work the way that they want to, following the leads that the experiments provide. That sometimes could work against me, as I have an aversion to hypothesis-driven research and grow uninterested when I have to follow the obvious next step. I prefer research that leads to unexpected findings and opens up more questions than the ones that it addresses. But once something excites me I am all in, and I try to explain to my trainees that there is nothing more exciting than going after a difficult question.

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

I was lucky to be exposed to distinct ways of thinking and doing science as I spent years in both the European and the US systems. Also, I learned a lot from my mentors, especially Harald. For example, I appreciated the importance of bringing together a team of people who are able to work together and at the same time bring different expertise and backgrounds. This is something that I adhere to even today. In my laboratory, you will find not only immunologists and stem cell biologists but also experts in *Caenorhabditis elegans* stress responses, mitochondrial physiology, RNA biology, and computational science, to mention a few. This mix can initially be somehow chaotic, but eventually it produces diverse and exciting work. However, in reality, postdoctoral training needs a serious update, as it doesn't prepare you for most aspects of your future independent career. You don't really know how to manage people. You are absolutely unprepared to deal with budgets and manage funding. And in most cases, you are not ready to communicate your science with the public and potential donors. Some institutions are doing a good job educating their junior faculty in such areas, but not all are successful.

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

The biggest challenge for me was how to connect my "basic" research to translational and clinical questions. It was indeed difficult to bring the "bench" closer to the "bedside," considering that I am not a medical doctor and unfortunately I do not see patients myself. And this is absolutely essential today if one likes to perform research with a wide impact. Although we are still struggling with this issue, the lab currently focuses primarily on human disease and addresses questions of direct clinical importance. One such example is our recent foray in mechanisms of drug resistance in acute myeloid leukemia (Chen et al., 2019). I am proud to say that a number of our basic publications have led to ongoing and future clinical trials in diseases like acute lymphoblastic leukemia, acute myeloid leukemia, and myelodysplastic syndromes.

What hobbies do you have?

Although we all spend most of our days in the laboratory or traveling to conferences, I believe that it is essential to have hobbies, and I have several of them. I am lucky to live in New York City, one of the world capitals for the culinary and art universes, so I eat a lot and spend Saturdays at art galleries. In a way, creative cooking is a form of art, and science has connections to both culinary practices (on the bench, we have to follow a protocol, or recipe) and art, as it depends on and showcases creativity. But at the end of the day, my hobby is my science. It is something that I love doing, gets me excited, and also gives me the pleasure of interacting with young people who are so impressive and driven—something that gives me immense pleasure. They are the future of science, and we are here to train them and nurture their careers.

Any tips for a successful research career?

To stop thinking about your career. To focus on things that matter. These are your trainees, your experiments, and the impact of your science; everything else will follow. I have never seen important and impactful science not get published or funded. And on the flipside, you can embellish bad science as much as you like, but readers and the scientific community today are sophisticated enough to discern the significance of the work.

References

Chen, X., et al. 2019. *Cancer Discov.* https://doi.org/10.1158/2159-8290.CD-19-0117

Tikhonova, A.N., et al. 2019. *Nature.* https://doi.org/10.1038/s41586-019-1104-8

Trimarchi, T., et al. 2014. *Cell.* https://doi.org/10.1016/j.cell.2014.05.049

von Boehmer, H., et al. 1999. *Cold Spring Harb. Symp. Quant. Biol.* https://doi.org/10.1101/sqb.1999.64.283