Interview with Costas A. Lyssiotis

Interviewer: Matthew Ward

Dr. Costas A. Lyssiotis is an Assistant Professor of Molecular and Integrative Physiology at the University of Michigan. A UM alumnus, Dr. Lyssiotis earned his bachelor's degree in Chemistry and Biochemistry in 2004, before going on to complete his PhD at

The Scripps Research Institute. His postdoctoral work was at Harvard Medical School with the laboratory of Dr. Lewis C. Cantley, and most recently he accepted an appointment at UM, starting his own group located in the Rogel Cancer Center. Find the lab on twitter @LyssiotisLab or at <http://lyssiotislab.com>

Matthew Ward (hereafter Matt): For the readers, what is your research focus?

Dr. Lyssiotis: My group works on understanding metabolic processes in human health and disease, and a lot of that work is done in the setting of pancreatic cancer. We study this disease from two perspectives: the regulation of cancer cell autonomous metabolic programs, and metabolic crosstalk pathways amongst the different cell types in a pancreatic tumor. A second area we've expanded into recently is understanding the metabolic properties of immune cells. The immune system is responsible for governing essentially all states of human physiology and pathophysiology, and is also regulated by metabolism, so we hope to tackle some of the difficulties of cancer through this window. The third aspect of the lab deals with building out mass spectrometry-based platforms as tools to study cancer and immune metabolism.

Matt: Would you please elaborate on that first aspect?

Dr. Lyssiotis: Of course! Returning to that first focus, pancreatic cancer is a disease for which the five year survival rate of 8% has not significantly changed in 40

years. So, clearly the things we're doing for other types of cancers, some of which now have survival rates near 99%, are not working for pancreatic cancer. So, we've asked ourselves: why is that? We think it has to do with the physiological properties of the tumor, like the extreme physical pressure which can be greater than ten times what is observed in a normal organ. This cuts off the blood supply, and thus oxygen and nutrient access by the malignant cells, which rewires the ways the cells in a tumor access fuel and, ultimately, their metabolism. Part of our work is mapping the re-wiring used by cancer cells to survive this harsh environment, and that's also where we look for therapeutic windows and drug targets. Bear in mind, however, that the tumor is also not just a mass of neoplastic cells. Around 90% of tumor content is non-malignant tissue architecture and stromal fibroblasts. We've found that several of these cell types are actually feeding nutrients to the cancer cells, and that by blocking this process we can blunt tumor growth without even touching the cancer cells.

Matt: How did you arrive at this interest, and what has been your path to success in your research career?

Dr. Lyssiotis: When I entered UM as an undergrad, I wanted to go to medical school because my mom said doctors are smart and make a lot of money, which sounded like a pretty good deal. I started taking pre-med classes, one of which was Organic Chemistry with Dr. Coppola, where I learned that I love chemistry. To foster this new passion, Dr. Coppola suggested that I get involved in basic research. Following his advice, I emailed faculty in the Chemistry Department . . . literally sitting in the Science Learning Center (this should resonate with the Chemistry majors), when I got an email from Professor Gary Glick. I went up to his office, interviewed, and he set me working with one of the faculty in his group. Actually, Gary was still here when I came back to work as a professor. Anyway, I worked with Gary for four years, did pretty well, published a couple papers, and wrote an honors thesis. Working in Gary's lab was out-

standing; we were studying how to inhibit the mitochondria to kill autoreactive immune cells, and blood cancers along those same lines. It got me interested in cancer, and in metabolism. I subsequently earned my PhD at The Scripps Research Institute working in chemical biology, and performed postdoctoral training with Dr. Lewis Cantley, still in a biochemistry theme—I was working in cancer metabolism, which was exactly what I wanted to do. That work ultimately led to the current focus of my research group. The University of Michigan has been the ideal home to pursue these ideas. Access to cutting-edge research/collaboration opportunities across disciplines has accelerated our progress, and the collegial support makes it a fun place to do science.

Matt: To what extent is collaboration across fields and disciplines present in your work, and what is your opinion towards collaboration at any stage of a research career?

Dr. Lyssiotis: Nowadays it is absolutely critical. I think collaboration is the key to progress. We're not going to find cures for cancer in just biochemistry—it would be naïve to think so. Since nobody can be an expert at everything, the next best thing is to collaborate with an expert. I try to live that truth in my lab: we are experts in biochemistry, tumor metabolism, mass spectrometry and metabolomics. My colleagues have built their careers studying their specific fields, and I'm never going to have the depth of knowledge that I need to answer the questions I'm asking in Immunology, for example, but I definitely have it in biochemistry. I would argue that

the big problems in medicine (and any others facing humanity) are going to require cross-discipline interactions. And, further, that when you take a step out of your box, and look at problems from others' perspectives, you come up with better ideas than you would alone.

Matt: What is your advice to undergrads with respect to a research career, both in getting started and continuing their training?

Dr. Lyssiotis: It's case by case, but a good rule of thumb is to find your passion. And, it's great if you can get started early for two reasons: one, you get exposed to research immediately to see if it suits you. That's the whole point of being an undergraduate: taking these risks and trying new things to see if it's something that sticks. The second reason is that starting early gives you a couple of years to actually accomplish something, to get involved with writing a paper or to get heavily into a project that you see through to a final product. That's a rewarding feeling; you get to figure something out that humanity never knew before you started.

As for getting involved, the best way is probably to browse faculty pages or their publications and find some areas of research/ideas that are of even moderate interest to you . . . and then email ten labs. Try ten and you are all but guaranteed to get a hit in one. Another avenue is summer fellowships, and that's a great way to jump into research in a more formalized sense. The other point I would like to make: at this stage, it doesn't have to be a perfect match. The idea here is just seeing what research is like on the ground floor, and to get exposure.