DR. JONATHAN STOKES

MACHINE LEARNING & NOVEL ANTIBIOTICS

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Dr. Jonathan Stokes is an Assistant Professor in the Department of Biochemistry and Biomedical Sciences at McMaster University. He received his BHSc in 2011 and his PhD in antimicrobial chemical biology in 2016, both from McMaster University. He then completed a postdoctoral fellowship at the Broad Institute of MIT and Harvard. In 2021, Dr. Stokes established his lab back at McMaster University, which, in part, leverages machine learning approaches to discover new antibiotics. The Stokes Lab also seeks to determine the molecular mechanisms underlying antibiotic tolerance and resistance. Furthermore, he is the co-founder of the non-profit Phare Bio, dedicated to navigating early-stage antibiotics through preclinical trials.

AS A HEALTH SCIENCES GRADUATE, HOW DID YOUR TIME AT MCMASTER INFLUENCE YOUR CAREER AND INTEREST IN THE BIOMEDICAL SCIENCES?

I was remarkably lucky since I was able to start working in laboratories at McMaster as a high school student. My entry into the lab began, oddly enough, as a gardener for world-renowned hematologist Dr. John Kelton at McMaster. As I was finishing grade 12, I guess he saw it fit to ask whether I wanted to spend a summer in his academic lab. At the time, I wasn't sure what to expect, but I ended up loving it and thought that it was the coolest experience. I was drawn to the laboratory environment and the camaraderie that existed within labs. Dr. Kelton was kind enough to also let me study under him through my first three years of undergrad. When fourth year came around, I ventured to explore a different field of study, and that's when I got into contact —through Dr. Kelton, actually— to Dr. Eric Brown, who is a world expert in bacterial cell physiology and antibiotic discovery. I did my fourth-year thesis with Dr. Brown, and that's when I realized that I truly loved studying infectious disease, antibiotics, and bacterial cell biology. I was just hooked. It was a pure chance that I happened to stumble into this field, but I was fortunate. Three weeks into my fourth-year thesis project, I realized that I wanted to do this forever, so I asked Dr. Brown if he'd allow me to do my Ph.D. with him, and he kindly agreed. [...] I suppose the question I asked myself, as an undergraduate student thinking about embarking on a Ph.D., was whether I could see myself doing this type of work every day for five years. The answer to that was, unquestionably, yes. That was all the self-convincing I needed before diving in. [...] Being in Health Sci was useful because there was a lot of elective space in the curriculum, so I was able just to fill up all my time with stuff that would enable me to spend more of it in the lab and explore topics that deeply interested me.

WHAT WERE SOME OF YOUR PAST PROJECTS, AND WHAT ARE YOU CURRENTLY WORKING ON NOW?

The project that I was given as an undergraduate thesis student with Dr. Brown was to look for small molecule

inhibitors of bacterial ribosome biogenesis. The ribosome is this big ribunucleoprotein complex that is responsible for translating mRNA into protein. We have a ton of antibiotics that inhibit translation, but we don't have any molecules that specifically inhibit the assembly process of the ribosome. So, the question was, can we find the molecules? In my undergrad thesis, I performed a chemical screen of roughly 30,000 molecules for those that inhibited the assembly process. Then, I spent the next two-and-a-half years —well into my Ph.D.— following up on one specific molecule that we were interested in and showing that it was a specific inhibitor of ribosome assembly. Proving that this molecule was inhibiting ribosome assembly and not translation, which is a tightly coupled biological process, took years of work. Indeed, those were tedious and complicated experiments. Then, after that, I felt like investigating a different biological system in bacteria. Through my work studying the ribosome, I got interested in the question, "How do you get antibiotics physically make their way past the bacterial cell envelope and inside bacteria?" This is called the permeability problem. Investigating the molecular features of antibiotic permeability made the second half of my Ph.D.

After this, I wanted to expand my research into systems biology and machine learning-type work, so I went to Dr. Jim Collins' lab at MIT, where I spent about 4 years before luckily being recruited back to McMaster. Indeed, it was at MIT where I started to get really interested in the application of artificial intelligence in new antibiotic discovery, which is what we're studying a lot in my lab now. We're trying to leverage the utility of machine learning to more rapidly get us to novel structural classes of antibiotics that we then have the ability to validate in the wet lab.

[...] Antibiotic drug discovery is inherently a multi-property optimization problem. For example, it's really easy to find molecules that kill bacteria in a petri dish. However, it's really hard to make an antibiotic that can be used in the clinic. That's because anything that's generally cell-toxic will kill bacteria, but it will also kill human cells, which is not ideal for a human medicine. So, when we're looking to use machine learning algorithms to predict new antibiotic molecules, or design new antibiotic molecules, these models need to be trained on a bunch of different molecular properties in order to satisfy all the molecular requirements that define a good human drug. These models are only as good as the data that we generate to train them on, so we take a lot of care to gather our own wet lab data to build the most robust models in the world.

GIVEN THAT YOUR RESEARCH CONCERNS DISCOVERING NEW ANTIBIOTICS, CAN YOU DESCRIBE TO US THE PROCESS OF CREATING A NEW ANTIBIOTIC FOR PUBLIC USE?

To develop an antibiotic in this space, soup-to-nuts, is about $1.5 billion. That's what it costs to develop any human medicine. However, for antibiotics, there's a fundamental economic problem in that there are very few financial incentives to develop antibiotics. That's because it's challenging to make a good return on your investment, relative to something like an anticoagulant that a lot of people are going to take daily for many years. However, to try to overcome some of the economic hurdles associated with antibiotic drug development, my previous professor, Jim Collins, and I co-founded this non-profit called Phare Bio. We built this non-profit entity to absorb a lot of the risk associated with expensive late preclinical antibiotic development. Our goal [at Phare Bio] is to take potentially useful antibiotic candidates from the academic laboratory and provide a viable economic path to get them through the preclinical drug-discovery process. By doing this, it will decrease the financial barriers to entering Phase I clinical trials.

HOW DO YOU BELIEVE THE FUTURE OF ANTIBIOTIC DEVELOPMENT AND RESEARCH WILL CHANGE BASED ON THE EMERGING INTERDISCIPLINARY NATURE OF THE FIELD?

In antibiotic discovery, I think that the widespread application of computational approaches will enhance the ability of my field to make significant progress. At least I hope so; I'm kind of betting my career on it. I think biology in general is becoming a data-driven science. You're always hearing about "big data" in biology-centric fields of investigation. For example, we are gathering genomics datasets at unprecedented rates that we are still trying to understand how to optimally analyze. Our ability to make sense of the vast quantities of data we generate will be important to make impactful discoveries. The challenge of having truly interdisciplinary work is that you have these teams of people, computer scientists, biologists, chemists, physicists, who don't speak the same scientific language. I mean, you talk to a computer scientist and they might not know the details of what a gene is, then they try to talk to me as a biochemist [primarily], and I don't understand the intricacies of graph neural networks. So, there's a language barrier, and overcoming that is not trivial. There's a lot of hard work on everyone's part that goes into making a truly interdisciplinary team that works collaboratively. But I think that will slowly happen naturally as the edges of all these scientific disciplines become blurred.

ARE THERE ANY MISCONCEPTIONS ABOUT ANTIBIOTICS THAT YOU WOULD LIKE TO ADDRESS?

Don't take them if you have a viral infection. They're useful if you have a bacterial infection, but if you have another type of infection, like the common cold, you aren't going to feel any better.