

Scott Wrighting: Welcome to the Three P's of Cancer podcast where we'll discuss prevention, preparedness and progress in cancer treatments and research. Brought to you by the University of Michigan Rogel Cancer Center. I'm Scott Wrighting.

In this episode, Rogel Cancer Center senior writer and public relations representative, Ian Demsky, sits down with Dr. Gotham Narula, chief of genetic medicine in the department of medicine at the University of Michigan Medical School to discuss how the COVID-19 pandemic has affected cancer research.

Ian Demsky: I thought we might start by just having you tell me a little bit about your research program and what questions you're trying to answer.

Dr. Gotham : I'm a professor of medicine here at the university of Michigan, and my research laboratory focuses on the development of novel, small molecule therapeutics to turn back on tumor suppressor proteins for the treatment of cancer. And we're specifically interested in protein phosphatase 2A, which is a tumor suppressive enzyme that the phosphorylates many key oncogenic proteins. And so it gets inactivated in a broad range of cancers, and we're trying to develop pharmaceutically tractable approaches to reactivate it therapeutically.

Ian Demsky: And what tools or sort of techniques do you use to answer those questions? So for example, if someone was to walk into your lab on a given day, what might they see your lab members doing?

Dr. Gotham : Yeah, so in terms of things we do in the lab on a daily basis, that kind of spans the spectrum from cell based assays, biochemical assays, testing enzymatic function of both normal and mutant proteins testing those then in cellular systems using lentiviruses and CRISPR based approaches. And then try and carrying them all the way through into mouse models of the disease, whether that be xenograph models or avatar patient derived the xenograph genetically engineered mouse models. And kind of collaboratively, we do a lot of chemistry as well as structural biology that kind of flows into the lab in the form of new compounds and new structures for us to analyze.

Ian Demsky: Can you take us back earlier this year when the university announced that research labs are going to have to close down due to COVID and what was that like for you and your lab members?

Dr. Gotham : So clearly we were all glued to the news with the announcement of COVID-19 and the subsequent restrictions placed upon doing biomedical research by the university, of course, rightfully so given the pandemic nature of the virus. And at first it was a major adjustment. And I think obviously you kind of went from going at a hundred miles per hour to going to zero. And people had to first go back and stop working and figuring out how to balance their personal lives and all of the impact COVID had it on them personally. I think for a lot of lab members in my group that took a couple of weeks to get to that sense of safety in their own home from this pandemic virus.



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And then it was after that a sense of, for many of us loneliness of feeling, not connected to our community, both the university community, our research colleagues here, as well as our lab mates and colleagues in the lab directly. And so a lot of what we tried to do was find ways to kind of mitigate that. So having virtual lab meetings, virtual journal clubs, virtual happy hours and check-ins and things to try to really deal with some of that isolation that COVID-19 created.

Ian Demsky: How did it affect sort of the research projects that you might have had in progress or perhaps things involving mouse models or other cellular cultures, things that you guys were working on?

Dr. Gotham : Yeah, I think that clearly it was a lab to lab based decision about what needed to be completely shut down and what needed to be wound down. I think given the nature of what we are hearing, we were a little bit more firm about it. And so all the cell based assays were just stopped any cell line that had been generated that was unique. We froze down into multiple different places. And then we were fortunate we didn't have any ongoing efficacy related animal studies that required multiple dosings to reach an endpoint. And so we really went into bare bones colony maintenance, then just to keep the current animal, transgenic strains alive and well.

Ian Demsky: During that period when your lab wasn't sort of physically able to get together, physically able to work in the lab. Can you tell me a little bit about sort of how your research efforts changed or whether there were any sort of creative opportunities to work in new and different ways that you guys discovered?

Dr. Gotham : I think the thing we're able to do differently or more creatively as one is we have a tendency to generate large amounts of data and not have time to actually sit down with it and think about it perhaps as deeply as we might want to at time. And so I think there's a lot of just pulling out old data and saying, "Wow, this was really neat. Maybe this could go in a paper or this could be a new project and things." So I think people really revisited some of their existing data in new ways. I think people in general read more of the literature. I think unfortunately in our hectic days that sometimes fall towards the lower end of what we do, reading new papers. And so I know a lot of the graduate students and postdocs read a lot more papers and were able to come up with some new ideas and new new projects and insights that they now are able to execute on, now that we're returning to a new sense of normal.

Ian Demsky: Was there anything interesting that you guys found going back in your data that maybe you hadn't analyzed yet or things that have spurred some future work?

Dr. Gotham : One of the things, for example, are there a series of mutations in this phosphatase that occur at the same amino acid that we've been studying, but are different than the ones we had actually functionalized. And we actually realized that some of those mutations in very specific tumor types and therefore my point to very different biology than the ones we studied. And we've already started to make some of those mutants and relevant cell lines and



consistent with our hypothesis. Interestingly, it does seem they have a very divergent biology, even though there at the identical amino acid level. Additionally we have some small molecules that we have been screening that were actually inactive. And so we kind of put them aside, but it turns out they might actually be almost dominant negatives on the target. And that turned out to be a potentially interesting new tool for us to use in the lab now.

Ian Demsky: What do you mean by dominant negatives? I'm not familiar with that term.

Dr. Gotham : When we look at, for example, small molecules that bind to a target, Ian, you can either turn the target on, or you can turn the target off. We're looking for ones that turn it on, but from just the chemical biology and tool perspective, the ones that turn it off can be highly specific tool for us to use. And so these molecules turn the protein off actually, instead of on. In fact, when I mean dominant negative is we co incubate them with the active ones, they actually prevent the active ones from working. So they're not just total loss of function, they also antagonize the active molecules in their function.

Ian Demsky: You might be able to use those molecules in future experiments to do what?

Dr. Gotham : To validate the specificity of the ones we're trying to develop. In other words, if you have a molecule that's almost structurally identical, but does the opposite of the one that activates it and you can compete out the activity with that same molecule in the cell, the likelihood that any biology you're seeing is an off target is incredibly small. So it's a powerful tool for validation.

Ian Demsky: Great. Now the research facilities have sort of reopened at U of M. But for somebody who isn't familiar with this sort of protocols and sort of what the new reality looks like, can you explain a little bit about what your lab looks like today compared to before COVID and how things are different?

Dr. Gotham : Yeah, so there's a couple of significant differences. One is we used to have a number of undergraduates at different levels of training, sophomores, juniors, and seniors who were in the lab. And right now undergraduates and volunteers are not allowed back in the lab. So the composition of the members in the lab have changed. Additionally, clearly we need to maintain social distancing. And so the number of individuals in the lab at any given moment is about 50% plus lower than I would normally see when I would walk around and talk to members of my lab. And additionally, we've gone to, as needed by protocol and mandate, shift based work so that people aren't overlapping in the times in which they're working. So for many postdocs and graduate students, that's meant less physical time in the lab. And so had to be in some ways more efficient in the time that they have in order to get the same amount of work that they'd like done.



- Ian Demsky: You know, I've read some articles and seen some other comments from some other faculty members. Do you see the way this is affecting undergraduates is sort of having a bigger effect on their sort of scientific careers or direction?
- Dr. Gotham : I hope that this won't last for long enough that it will have a longterm impact on undergraduates desire to do biomedical research and medicine. Actually, what I do hope is once it's appropriate from a safety perspective, that they'll return in greater numbers than ever because they'll realize that the only way we'll ever deal with these pandemics is not through politics, but by through medicines and by science and great hospital systems like our own. So my hope is longer term, it will be good, Ian, for biomedical research and clinical medicine, but in the short term, it definitely creates challenges. In fact, I think the group that's the most perhaps vulnerable are our graduate students, where there's a very finite time they have in the lab and they have a set of expectations associated with it that will be more difficult to meet.
- Ian Demsky: And then just maybe taking a step back a little bit further, can you reflect maybe based on your own experiences or other cancer researchers that you've known and talk to about sort of how COVID is impacting the cancer research community more generally?
- Dr. Gotham : I think that many of us who have ongoing collaborations with colleagues have come to a stand still and in some places and even a harder ways than our own, and particularly hearted areas, for example, of New York and others. I think that it's a community there's significant numbers of meetings in which we're able to gather together and discuss new ideas. While Zoom is a wonderful platform or BlueJeans at some level, I still think face to face interactions are critical for starting new projects and collaborations. And many of our majoring Ian, cancer meetings have been canceled as you know, or have gone fully virtual, which doesn't allow for as much of that networking and socializing. And I think therefore some of the germination of those new ideas and collaborations have been affected.
- Ian Demsky: Yeah. I mean, I think to a lot of people out there in the general public or our patients we see at the cancer center they know that people are conducting research into cancer, but for them it's just kind of a very nebulous abstract thing. So I think anything that we can share, talk about that sort of helps people to understand sort of specifically what this means for actual cancer researchers or to actual labs can be really helpful. So I don't know if you have any thoughts on how this is affected effecting people, faculty working the ground and other other lab members, or important takeaways or lessons that might be learned from this overall experience.
- Dr. Gotham : Yeah. I mean, clearly I think there is research that's very basic and mechanistic that's fundamentals in the longer term to the discovery of new drugs and treatments for our cancer patients here at the Rogel Cancer Center. I would tell you that there's also more immediate work that is kind of in the later stages, which we hope will get to the clinic in the next day, two years. And so if we



think of a two year timeline for one of our cancer patients, and now we've had a delay of a year that effectively a drug that we don't know, but if it was efficacious and safe, then it would be delayed a year to get to our patients. And I think those are the tangible things that we're really struggling with. I mean, we do a good amount of drug development of my group and collaboratively in the cancer center here. And we had that sense of urgency because we're getting closer to the clinic with some of these small molecules. And there's no doubt that this period has slowed that process down.

Ian Demsky: Have you seen like postdocs or graduate students or other members of the lab sort of maybe coming together in new ways or working with each other outside of that lab context and new ways that that is sort of forced upon them virtually or creative problem solving on their part?

Dr. Gotham : I mean, one of the things that always amazes me about our students and our postdocs and such is the resilience in the face of adversity. And I mean to answer your question directly, and I think they have come together in new ways. I mean, one thing I've noticed is there's a lot of, and this might sound paradoxical, more socializing. And what I mean by that is it's almost the isolation created by being alone that makes them get on more Zoom calls together, talk to one another together, run experiments by one another and such. I've seen a lot of that more cross pollination and discussion than previously where they're much more kind of with their blinders on to get their work done and such. And so in some ways it's created, I think, new opportunities to communicate and socialize albeit virtually off times.

Ian Demsky: Any, anything that we didn't touch on as it sort of relates to what your lab has experienced and the scramble to get everything shut down and then this weird transition period, and now sort of ramping back up that you think might be interesting or important for folks to understand?

Dr. Gotham : No, I mean, I think the logistics of it we've gone over, I think some of the challenges and opportunities it presents. I think one of the unknowns and that's the hardest thing for us to deal with is, as people I think is the unknown, is whether there'll be a resurgence of this virus and whether we'll have to shut down again. And while we'll have learned from what we did previously, I think each time we do that it will be more and more devastating to cancer research even to patient care for our cancer patients. I mean, a lot of them had to defer treatments and defer visits because of COVID-19. And so the impact goes beyond the live loss directly to the virus, but also to lives affected by the fact that their care has to be deferred.

Probably, I should leave more on a message of hope, perhaps. Which is that I think this will hopefully for a new enthusiasm to support research by our government. And it already appears that with this a year than IHI budget, there's more monies for biomedical research. And as we talked about, hopefully people see what pandemics can do, but what also great medicines and vaccines



and therapeutics can do that more of our undergraduates and high school students will go into research and medicine.

Ian Demsky: Yeah. We've certainly seen a great increase in the kinds of content and interest in the research that's being done and the patient care that's being done here at Michigan Medicine since the pandemic started. And I think the public is hungry for content and information about what our researchers are doing, what our doctors are doing, trying to figure out this pandemic. And so perhaps some new interest has been sparked in biomedicine through all of this.

Dr. Gotham : Yeah, no, absolutely. And I do agree with you if you brought up, it can sometimes seem like a black box. So the more chances we have to kind of explain it, I think the better it is for the community as well as for hopefully future physician scientists and healthcare providers.

Ian Demsky: Great. Well, I really appreciate you taking some time to discuss this and to share your experiences more broadly with our Rogel Cancer community.

Dr. Gotham : It's a pleasure, Ian.

Scott Wrighting: Thank you for listening and tell us what you think of this podcast by rating and reviewing us. If you have suggestions for additional topics, you can send them to cancercenter@med.umich.edu, or message us on Twitter @UMRogelCancer. You can continue to explore the three P's of cancer by visiting rogelcancercenter.org.



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