COVID Information Commons (CIC) Research Lightning Talk

Transcript of a Presentation by Sarah Bowman (Hauptman-Woodward Medical Research Institute, University at Buffalo), January 2022

Title: RAPID Enhanced SARS-CoV-2 High-Throughput Crystallization for Structural Studies

Sarah Bowman CIC Database Profile

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Youtube Recording with Slides

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Transcript

Sarah Bowman:

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And can you see my screen?

Florence Hudson:

Yes, we can hear you, we can see you, looks great.

Sarah:

Perfect. Okay. Well, you know, I want to first of all say thank you for this opportunity to come and talk to kind of the CIC webinar - on the CIC webinar again, I'm excited to have a chance to update everybody on the progress we've made since, I think October 2020, is when we first - when I first gave a talk. So my RAPID award is for *Enhanced SARS-CoV-2 High-Throughput Crystallization for Structural Studies*. And I am the Director of National High-Throughput Crystallization Center located in Buffalo, New York.

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And so, the first thing you might want to ask yourself is: what is structural biology? And structural biology is really the study of the structure of what the different proteins or the pieces and parts of the SARS-CoV-2 virus and other things look like. So everything I'm going to tell you about today is about the

SARS-CoV-2 virus. And what you can see, can you see my pointer? Great. You know, everyone is very familiar with the ball with the red dot spikes poking out of it, and that, that is the SARS-CoV-2 virus. Obviously, it's quite a bit smaller than this. And the red spikes coming out are actually what's called the spike protein. And that's what the vaccines are designed to kind of interact with. There are a large number of other proteins that are encoded by the viral genome. And our goal in structural biology is to understand what those structures look like, so that we can then design therapeutics and drugs for actually fighting against those things. So one of the major ways to do this is through a technique called macromolecular X-Ray crystallography. And in crystallography, what we do is we take our protein samples, we have to screen them through many different conditions to find the ones that will generate a crystal, once we have a crystal, we can shoot X-Rays at it, do a bunch of other stuff and solve structures. And those are what you're seeing here in these big cartoons on the screen. My lab actually focuses on this, this point right here, which is the bottleneck in this whole process, which is finding the conditions that will make a crystal.

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And so what we do is we have a high-throughput pipeline, we're the only facility in the world that actually has this ability to do 1,536 different conditions in one experimental assay. And we provide robotics imaging instruments and expertise. We've been running for 21 years. We monitor for crystal growth over time. And so the first thing we do, what I'm showing you here, is one well out of the 1,536 monitored over one week, we take pictures of that, it's kind of like looking at pictures with your cell phone, except we have to zoom in quite a bit more closely to be able to actually see what's happening here. And then we also have additional imaging modalities that help us really quickly identify these crystals. And so we're not going to go into these details. But we have a very unique setup, essentially, these - these actual images are from the first sample that was sent to our lab in, actually was sent in March of 2020. And was supported by the NSF RAPID that we received and the first structure that came out of our user groups. And so I'll show you the structure momentarily.

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So at this point, two years in, we have now crystallized a lot of different Coronavirus proteins for structural studies. I'm showing a snapshot of six different proteins from six different groups across the country. And you can see for each of them that there are three different imaging modalities. Some of these look like what you would consider to be crystalline, like these nice little crystals, and some are harder to see. But with our imaging modalities, we can very quickly see them. And that's part of why it's a very efficient, rapid way to do this.

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So we have, like I said, crystallized a lot of Coronavirus proteins, and our users who send us samples from all over the country at this point all over the world have generated a lot of structures. And so at the top here, I'm showing four different representative structures from users who have sent us samples. Many of these contain inhibitors. So this is a potential inhibitor for the SARS-CoV-2 main protease, it's a major therapeutic target. This is a portion of the spike protein with a potential nanobody that could help

interact with it. And so at this point for our outcomes, we have had 33 user structures deposited to the protein data bank and of those 33, we've got 24 potential inhibitors and one nanobody. Eight of our users have published papers so far. And we are actively working on more samples. We actually, literally while I was on the, signing in today, I was finding out that we've got four more samples coming next week. So this is a continuing operation where we are - we're providing these services.

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The other thing that we've been using our RAPID funding for is actually to help us to do a little bit better with our data. So when we do high-throughput experiments of any kind, you produce a tremendous amount of data. And for us, that means about 14,000 images per sample that we receive. And so we actually have built a particular software graphical user interface, which we call MARCO Polo. It incorporates a machine recognition of crystallization outcomes. And it was actually built by a very talented post baccalaureate student, Ethan Holleman, who's now a graduate student at UC Davis. And you can see that we've got our 1,536 platform, we can zoom into certain areas, we can watch crystals grow over time, we've got a tremendous amount of metadata. And so, it enables - it also really helps enable collaboration because we can, we can share this information with, with our users. And so we're really excited about the software.

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Another thing that I'd love to kind of get across is that structural work has been absolutely critical in the past two years for the development of both the vaccines and therapeutics or drug treatments against SARS-CoV-2. So I showed at the beginning an illustration of some of the structures that have been solved. And at this point, many of the proteins that are encoded by the SARS-CoV-2 genome - we do have structures, we have many of these structures in different kinds of states with different things found. And in fact, my collaborators at HWI Dr. Lynch and Dr. Snell and I wrote this paper a couple of months ago, actually detailing what the contribution of structural biology has been to the SARS-CoV-2 pandemic.

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And as a highlight of that, I'd like to highlight some of the work done by my HWI [Hauptman-Woodward Medical Research Institute] colleagues at the IMCA-CAT beamline at APS at the Advanced Photon Source outside of Chicago. It's a beamline that actually works with some of the major pharmaceutical companies in the world, including Pfizer. And as many of you, I'm sure, are aware, the FDA has recently approved Paxlovid. And this is the structure of Paxlovid. It is a inhibitor for the SARS-CoV-2 main protease and the defraction data that was collected to be able to solve the structure of what this actually looked like, and helped design this drug was collected at the IMCA-CAT beamline that we direct at HWI.

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So finally, you know, one of the unique things about COVID-19 has been that it's been, of course, really terrible, but also a really amazing time to be a scientist and to do outreach and talk about science. And so, you know, one of the first things that, you know, I was able to do with the work that we were doing was actually the CIC lightning talk in October 2020. I have since done podcasts, interviews, including

being featured the day after the Super Bowl on the front page of the Buffalo News. We actually had a student who photoshopped that to put a crystal over the Lombardi trophy. We've been active in social media, I've been happy to be able to participate with CIC and other talks as well, including at the NIH, we've had a lot of student engagement.

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And then very, most recently, we actually were visited by Raven the Science Maven, and any of you who are familiar with her work, she's a science communicator. And we did some crystallization experiments in the lab, which were then featured in *The Washington Post*. So we're really excited about the work that we have been doing against SARS-CoV-2. We're so excited about the structural biology efforts kind of worldwide that have helped to kind of really address what the proteins in the SARS-CoV-2 virus actually look like.

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And with that, I will, you know, thank you for your attention. Thank our crystallization center users which come from, they come from all over the world. We've had a lot of people from all over the country actually make use of our services for screening. And we're very grateful for our funding from NIH, GMS and from NSF. And so thank you for your attention. I look forward to getting any questions after everyone else's talked. Thank you!