COVID Information Commons (CIC) Research Lightning Talk

Transcript of a Presentation by Sarah Bowman (University at Buffalo), October 16, 2020

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

Sarah E Bowman CIC Profile

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YouTube Recording with Slides

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Transcript Editor: Macy Moujabber

Transcript

Sarah Bowman:

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Okay so I'm going to tell you a little bit about the work that we're doing at the Crystallization Center at HWI with our RAPID to enhance- for enhanced high-throughput crystallization for structural studies.

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So, we'll actually start with a figure that probably many of you are familiar with from the CDC [Centers for Disease Control and Prevention] where you can definitely see structures of different proteins like the big red threatening spike protein and of course this is one SARS-CoV-2 virus. What we do in structural biology is- what we're trying to get at is what do these structures actually look like at a molecular level detail? Because if we can get at that information we can do better at designing things like vaccines and therapeutics and ways to actually treat what is happening at a very molecular level.

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So one of the things that's a little tricky is that viruses are really small and so I just want to give you a framework for thinking about how we look at things like the proteins that are part of the virus. So if you- this is a width of a single human hair, and we can then move down in scale to a grain of pollen, a single red blood cell, an aerosol droplet, all the way down to one SARS-CoV-2 virus. And this is part of why it can be difficult to really probe what the pieces and parts of the virus- the proteins actually look like.

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We use structural biology to do that. So this is a SARS-CoV-2 genome. We're really not going to go into this in any detail, but what is really awesome is that we've already done a lot of work as structural biologists in already determining structures of a number of the proteins that exist that are encoded by the viral genome. So essentially 29 different proteins are encoded. A number of structures have already been solved. And again, the reason why we want to work on this is because these are- the red arrows indicate particular targets for possible treatment and vaccine development. So in the Crystallization Center, the way we do this is actually by doing x-ray crystallography. So in x-ray crystallography, we do a crystal- we have a crystal of our sample. We shoot x-rays at it. We get electron density. And we end up being able to get a model of 3D coordinates. One of the actual big bottlenecks there is actually determining the conditions that will generate the crystals.

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And so that's what we specialize in at the Crystallization Center. We do high-throughput crystallization screening trials. So we have 1,536 conditions in one microassay plate. So this is very efficient. Less sample is required and we have a lot of imaging and robotics and expertise to be able to do this. We've been in operation for 20 years. So our NSF RAPID has really funded this remote mail in sample, being from all over the US for crystallization screening experiments for SARS-CoV-2 proteins.

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So we're really excited about being able to do this, and we've been really working as a resource for structural biology, and what happens is we monitor these wells, each of these wells over time using a lot of different imaging modalities.

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So one of the things that our RAPID award actually funded was development of a graphical user interface for all of these crystallization images. So I had an absolutely wonderful student working with me over the past 12 weeks and developing this GUI that incorporates an automatic scoring algorithm that we developed in collaboration with Google Brain and pharma companies and HWI. And so we're literally about to submit this manuscript describing the software, so we're very excited about that.

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And we've also been doing a lot of successful screening of a large number of SARS-CoV-2 samples. So we've had people from all over the U.S. sending us samples of their proteins, sometimes proteins in complex with a drug - a potential drug, and we are screening those, getting great results with the crystals, and some of those have already generated structures such as this. This is an example of the

SARS-CoV-2 Mpro protease which is a main drug target. We've actually got a number of structures that are in publication or on bioRxiv already. And so we're really excited about the work that we've been doing.

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We definitely are interested in if you have samples that you're interested in screening for protein samples for crystallography, please get in touch. You can check out our website or Twitter handle and we do have a structural biology channel on the Slack COVID Information Commons and so please feel free to check that out. Thank you.