COVID Information Commons (CIC) Research Lightning Talk

Transcript of a Presentation by Xiaohong Tan (Bowling Green State University), June 11, 2024

Title: SARS-CoV-3

Award CIC Database Profile

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Transcript

Xiaohong Tan:

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So today I'm going to give a talk about SARS-CoV-3. My name is Xiaohong Tan, you can call me XT, and I'm at Bowling Green University in Ohio.

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Before we begin talking about SARS-CoV-3, let's just briefly introduce or just briefly touch on the world wars. Everyone knows WWI and WWII - when will we have WWIII? No one wants it and as a biochemist, my lab can do nothing for WWIII, but my lab can do some work for SARS-CoV-3.

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In the past 20 years, we have already had three outbreaks of this beta coronavirus - SARS-CoV-1, MERS-CoV, and SARS-CoV-2 is still here. In the last 20 years we have already had three, so it is highly possible that the next beta coronavirus, for example, SARS-CoV-3, might come in the next decade. We still remember how bad it was when SARS-CoV-2 arrived - many people died and it was very isolating. It is extremely important that we have tools to fight SARS-CoV-3 in advance. It will save a lot of lives. The purpose of my talk today is how we can design a tool for SARS-CoV-3 in advance.

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What could be SARS-CoV-3? If we look at the coronavirus family tree, I put the future possible SARS-CoV-3 just after SARS-CoV-1 and SARS-CoV-2. I have to highlight for the past, SARS-CoV-1, SARS-CoV-2, and MERS-CoV mostly all belong to the betavirus lineage.

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This is a spike protein for a betacoronavirus. Here is a Delta and an Omicron for SARS-CoV-2. It contains two domains, S1 domain and S2 domain. So you can see, S1 domain contains lots of mutations, as indicated by these color dots. If you look at S2's domain, however, it's highly conserved. So if you compare the S2 domain of the past three beta coronaviruses, you can see among their three of the S2 domains, the amino acid sequence is highly conserved and the structure doesn't change. Therefore, I hypothesize if we have SARS-CoV-3, it is highly possible that we will have SARS-CoV-3 whose S2 domain is without changes. That means we can target only highly conserved S2 domains to find the [?] to fight the future SARS-CoV-3.

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Many labs, industry or academic labs, are designing tools to fight the spike protein. For example, antibodies can attack the spike protein and prevent it from bending the human receptor. In my lab, we designed the DNA-based aptamers into the spike protein.

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So what are aptamers? An aptamer is a single-stranded oligonucleotide. It's a single-strand of DNA. They can form into complex 3D structures and enable us to recognize different targets. Compared with antibodies, aptamers have many advantages. One significant advantage is that DNA aptamers are very low cost so compared with antibodies, it could be 2,000 times cheaper. If we can have such low-cost tools battling the spike protein, we can have very useful tools.

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As I said before, we want to target the highly conserved S2 domains and find them with DNA aptamers. Let me briefly touch on the S1 domain. A spike protein has an S1 and S2 domain - two domains. We want to target the highly conservative S2 domain. The S1 domain contains a very famous re-binding domain called RBD. This part of the spike protein is how the virus recognizes human receptors. This is, of course, the most popular target for research, but you cannot approach this as a universal target because even among SARS-CoV-2 Delta or Omicron S1 domains, they are highly mutated. So are instead targeting the highly conservative S2 domains. So we use an aptamer selecting approach.

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And we finally opt to a single strand of DNA. So this is the structure and the sequence. We measure the binding affinity to be a low nanometer range. So this is a very good binding affinity.

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How about the binding specificity? We used a colorimetric assay. In this assay, you can see, if you add the target protein, the color will change to purple. Without the target protein, for example, nonspecific proteins, the color remains red. So if we add the S2 protein, this is our selection pattern of changing color, if you add the whole spike protein which contains the S1 domain, the S2 domain of SARS-CoV-2, it will change color. If you add the SARS-CoV-1 spike protein, it also changes color. This was not a surprise to us because as I said before, the S2 domain is conserved. So for the SARS-CoV-1 and SARS-CoV-2, they have a very similar S2 domain and so the aptamer can recognize both. If you test other nonspecific background proteins, you can see the color red remains, especially for the S1 domain. This data clearly shows us that we have higher affinity binders which can specifically recognize the S2 domain of different betacoronaviruses.

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So next, we check the inhibition efficiency. So briefly speaking, if you coat the human receptor here and add a spike protein - in the substrate, you will see the color. If you add inhibitors and prevent the spike protein from binding to the receptor, you see weak or no color intensity. So if we assume that no aptamers is 100%, we test the negative, random aptamer sequence and see there's no inhibition. We then test the positive control and this is reporting the DNA aptamer. We know this one can bind to the S1 domain. And we target to the Y type SARS-CoV-2 here. And it can block close to 70%. So how about our aptamers? It looks very similar to the positive control. It also can block the spike protein to recognize the human reception.

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This actually was surprising data to us because as I said before, the aptamer was about the S2 domain and it is where the spike protein uses the S1 domain to bind with the human cells. So, why is it that binding in the S2 domain can affect the S1 domain's binding to human cells? Here is a hypothesis. Based on the structure data, we know that if the spike protein needed to bind to the ACE2 receptor, [?] needed to open. So our hypothesis is that once S2 binds here, it might have a [?] effect to prevent this S1 domain from opening. So that's the hypothesis. But unfortunately, we worked very hard at this with our collaborators and try to use the COVID structure but the [?] complex folding structure is very difficult to resolve. One partial reason is because the aptamer is a single stranded nucleotide. They are highly flexible. So we don't have a structure of data so far, but this is our hypothesis.

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The conclusion is that we report the first anti-S2 aptamer. It has an RBD-independent approach to inhibit the virus using spike proteins that recognize the human cells. And because the S2 domain is highly conserved, we believe now we have a tool in advance to fight SARS-CoV-3. Maybe in the next decades, when SARS-CoV-3 comes, we will have this aptamer which can be designed as a bioanalytic tool or used as a therapeutic tool to fight the future of SARS-Cov-3.

By the way, I have to mention that we reported the first anti-S2 aptamer and afterwards, people reported the anti-S2 antibodies. They observed that using the anti-S2 antibody can also block the virus that infects human cells. But I have to say our aptamer is 2,000 cheaper than antibodies.

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So I'd like to take this opportunity to thank the NSF and BGSU for providing me with support. Thanks to the Tan Group at BGSU, especially Dr. Achut Silwal, he finished most of this work and right now is at Columbia University to perform his second post-doc. And thanks to my collaborator Prof. Saurabh Chattopadhyay for for the structures and analysis. Thank you so much.