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MIND, BODY & SOUL Part II:
Innovations in Prevention, Treatment, and Sustainability

Novel Approaches and Platforms for Treating Disease
Part II: Comprehensive COVID-19 Solutions

Henry Ji, PhD, Chairman, President and CEO, Sorrento Therapeutics, in conversation with **Max Gomez, PhD,** Senior Medical Correspondent, CBS2 New York

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Introduction:

While cell therapies have generated much excitement due to their diverse and robust potential in regenerative medicine, many biotech companies have taken what could be called a reductive approach. Rather than entire cells, they're working with molecules that are a different type of immunotherapy. This class of drugs has been around for some time in the form of monoclonal antibodies for therapeutics, diagnostics, vaccines, and more from pharma giants like Amgen, Genentech, GlaxoSmithKline, Bristol Myers Squibb, and dozens of others. Regeneron and Eli Lilly have made headlines with their monoclonal antibodies for COVID-19. More recently, in an effort to improve on the effectiveness of monoclonal antibodies, companies have explored where to group together as small molecules, although some are still quite large.

One such class that is truly a novel approach to treating disease is called bispecific antibodies. These compounds allow binding to two or more different receptors, potentially bringing together disparate targets and effectors, either cellular or molecular. Roche, Merck, and AstraZeneca are exploring their use beyond oncology to include a wide range of applications, from autoimmune disorders to arthritis, psoriasis, and asthma.

But other truly small molecules are also seeing a flood of research interest in drug development. They've been called a revolution in pharmacologic chemistry because of their many unique mechanisms of action in diverse applications. A unique small molecule class that has been dubbed the next blockbuster therapy goes after what were once thought to be undruggable targets, disease-causing proteins. Targeted protein degradation utilizes small molecules to destabilize such pathogenic proteins by tagging them for dismantling by normal intracellular processes. While virtually all major pharma companies have a stake in this class, smaller biotechs, such as C4, Arvinas, and Kymera, are also actively pursuing its use.

Few companies have as large a presence in the small molecule therapeutic and diagnostic space as Sorrento Therapeutics. Henry Ji, Sorrento's president and CEO, joins us now to discuss their technology.

Max Gomez, PhD:

Henry Ji, chairman and president and CEO of Sorrento Therapeutics, welcome. Henry, this is really an exciting time for your company and in research here in general. I know that Sorrento is involved in diagnostics, prevention, early intervention, rescue therapies for a variety of different diseases if you will, but let's talk about the hot one at the moment. What's your approach, a comprehensive solution if you will, for COVID-19?

Henry Ji, PhD:

So, hey, thanks, Max. And our solution to it is detect early, treat timely. Treat timely means that at different stages of COVID-19 disease, you treat with different measures or treatment solutions. So, for example, we have the COVID-19 rapid antigen detection system called COVISTIX, and we can detect whether you have the infection in as short a time as 2-5 minutes. Moreover, if your test remains negative for 15 minutes, you can proceed with your normal activities. With COVISTIX, we can detect virus in patients between symptomatic days 1 and 7. The moment you have symptoms, you say, "Okay, I'm infected. Now what's the solution? What's the next step?" The next step in treatment of infected individuals we are developing at Sorrento is a neutralizing antibody. Neutralizing antibody treatment is among the most effective ways to treat the COVID-19 infection because the antibody binds and prevents viruses from entering cells, which potentially results in decreased virus replication and spread within an infected person.

We are developing three ways to administer neutralizing antibodies. One way is to deliver the antibodies by IV. Our IV administration is designed to require only 2-5 minutes, which will conserve the hospital resources currently required for one hour or five hour infusions. The idea is to provide treatment solutions that are easily delivered in an outpatient setting. Our second form of neutralizing antibody administration currently in clinical trials makes use of nasal drops. This allows direct delivery of the antibodies into your nose, blocking the virus entry into the cells of the epithelial layer in the nose, and potentially inhibiting viruses from replicating in this area and spreading into other regions of the respiratory tract.

A third means of delivering neutralizing antibody to patients currently in development at Sorrento is by injection of a DNA plasmid encoding the antibody into your muscle. The cells that make up your muscle would then express the neutralizing antibody in your body. We are currently completing work supported by government contracts for this this program. DNA-encoded antibodies provide a very rapid means of addressing the treatment challenges posed by emerging variants of concern during a pandemic. Public health officials are focused on the worldwide circulation of virus variants of concern first identified in the UK, Brazil, South Africa, and India. We recently finalized an exclusive licensing deal with Mount Sinai to co-develop antibodies that cover each of the known variants of concern. We are combining the neutralizing properties of antibodies discovered at Sorrento and Mt. Sinai to develop a cocktail of two antibodies in each of our three delivery systems for treatment of infected individuals.

Max Gomez, PhD:

Henry, let me ask you the diagnostic part of it. How was that administered? What do you use for that now?

Henry Ji, PhD:

Oh, the test is very simple. You do a quick nose swab. It's not a deep nose swab, but rather shallow. You then place the swab into a lysis buffer and pour the resulting mixture into a detection cassette. The test provides your positive or negative result within a few short minutes.

Max Gomez, PhD:

So you mentioned also then that this cocktail that you're testing, that can be administered a variety of different ways. How is it that this can cover all of the different variants then, since we keep hearing that the variants are very specific for the vaccines? How is it that this covers the different variants?

Henry Ji, PhD:

Because we have tested our antibodies for neutralizing activity against the variants. We have each of the viruses considered variants of concern, or VOCs, and we have their respective Spike proteins expressed as a recombinant protein. If any antibody in our collection binds and neutralizes one or more variant of concern, we can use that antibody as a component of a two-antibody cocktail that provides coverage against all of the virus variants of concern. We are already pushing a cocktail through development that potently neutralizes each of the known variants of concern. This cocktail contains two antibodies, STI-2020 and STI-5041, and these two antibodies provide potent neutralizing coverage for all of the currently identified VOCs. We know the virus will continue to evolve as infection numbers increase, so we are focusing our efforts on developing a full panel of antibodies to potentially provide coverage against future virus variants.

Max Gomez, PhD:

And as new variants pop up, do you manufacture these new antibodies or how do you then decide what to put into the cocktail?

Henry Ji, PhD:

We believe right now we have an antibody cocktail that provides potent neutralizing activity against each of the current variants of concern. Manufacturing of the antibodies in this cocktail is ongoing. As new variants emerge, we will continue to monitor for gaps in coverage by our antibody cocktail and explore new antibody combinations from our current collection of preclinical candidates to address those gaps. We can initiate manufacturing activities for any antibody in our collection within weeks, and we can use this capability to enable our antibody delivery systems and meet the treatment challenges associated with any emerging variants of concern. Our treatments and diagnostics for mild and moderate COVID-19 will include those that you could access at your local pharmacy and those that

are administered in an outpatient setting. Our vision is to allow those who receive a positive COVISTIX result to access COVIDROPS or COVI-AMG neutralizing antibodies to treat their infection.

It's worth mentioning here our work on therapeutics for use in treatment of moderate to severe COVID-19 cases in the ICU. Oral administration of Abivertinib, a Bruton's tyrosine kinase inhibitor, is designed to decrease the effects of cytokine storm in the context of COVID-19. We are currently conducting Phase I clinical trials with Abivertinib, and we have enrolled over 300 patients in both U.S. and Brazil, thus far. We are also in discussions with the government of Mexico around extension of these trials into hard-hit regions of the country. We are working to determine if Abivertinib can help to more quickly discharge COVID-19 patients experiencing moderate to severe COVID-19 from the hospital. In clinical situations where ICU patients require oxygen and intubation on the ventilator, Sorrento is investigating the clinical safety and efficacy of treatment using adipose-derived mesenchymal stem cells. To date, each of the ten patients who has undergone this treatment, which requires three infusions, has been discharged from the ICU. After the first infusion, many of the patients' conditions improved; they reported feeling much better and they required less supplemental oxygen. After the third infusion, some patients were immediately released from the hospital. We're talking about patients being discharged from ICU and discharged from hospital on the same day. Very impressive.

Max Gomez, PhD:

This sounds obviously very exciting. And it sounds like you have the capability to develop some of this for other viruses or even other diseases, infectious diseases, and going on to cancer. How else will you use this platform?

Henry Ji, PhD:

We have taken a human antibody library approach. This approach does not require the use of recovered patient samples. Rather than relying on B cells isolated from infected patients to identify candidate antibodies, we can use our molecular libraries that already encode billions of antibodies to screen potentially neutralizing antibodies for any pandemic threat pathogen target.

Let's say that in response to an actual outbreak or as part of a pandemic readiness program, a decision is made to develop antibodies that neutralize Nipah virus. We can screen against Nipah virus proteins and isolate candidate neutralizing antibodies within a two-week timeframe. These antibodies can be developed as traditional protein therapeutics or we can encode the antibody sequences on DNA plasmids for intramuscular administration. DNA plasmids of this type can be manufactured very quickly, and within a month we could have a therapeutic ready for use in the clinic. This type of rapid response capability is aligned with the mission at DARPA and they have supported us with a contract to develop this technology as a COVID-19 response that could readily translate into use for protection and treatment of existing or emerging pandemic threat pathogens.

Of course, this technology can also be used for protein therapeutics in the oncology and metabolic disease spaces. Use of DNA plasmid-based technology to express immune checkpoint inhibitors or enzyme replacement therapies would provide innovative options

over the established use of manufactured protein for these purposes. Plasmid DNA-directed expression of biological therapeutics in patients can be a novel and valuable means of achieving long-term treatment solutions while minimizing the burden of treatment on patients and health care providers.

Max Gomez, PhD:

You have so many different possibilities here within the company, how do you decide what to focus on? You know, the saying that a Jack of all trades is a master of none. How do you decide where to really put your energies as a company?

Henry Ji, PhD:

We have a great deal of energy and drive at Sorrento. We have a healthy portfolio of projects and strong support from public equity, cash holdings, and government contracts to support multiple ongoing efforts to bring products to market. This has allowed us to develop products that are now at various stages of clinical development. On the diagnostic side, we have already submitted our EUA for COVISTIX. If the FDA give us a green light to proceed, we are ready to enter the market, which should provide us a revenue stream. Our neutralizing antibody is currently in Phase 2, as is Abivertinib, and our mesenchymal stem cell therapeutic. EUA approval around any one of these programs will serve to further increase our revenue and fuel our push to master the trade of developing therapeutic and diagnostic solutions across a wide selection of human disease areas.

Max Gomez, PhD:

So you can chew gum and walk at the same time.

Henry Ji, PhD:

Exactly. That's the plan.

Max Gomez, PhD:

Henry Ji, thank you so much for your time. It sounds very exciting. And we look forward to hearing more about it.

Henry Ji, PhD:

Thank you very much, Max.