Salvagene GROUP

Business Unit: SARS-CoV-2 Task Force
Keynote: #20

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Salvagene SARS-CoV-2 Task Force: The quest for new weapons to combat Covid-19.

NEW!

Dear Premium Customers,

In our first podcast, we present some of the new technologies behind potential Covid-19 therapies to complement the solutions already outlined in our Keynote series. We see them as, at best, a bridging solution while we wait for a future vaccine to become globally available.

In the race between man and virus, researchers are adopting completely new approaches to putting the treacherous coronavirus back in its box. These include stem cells from the placenta, antibodies from the blood of recovered patients and countermeasures against the dreaded cytokine storm.

As we reported in Keynote 17, remdesivir is the first effective medication for the treatment of Covid-19 symptoms. But the

search goes on. This also involves branching out in some unusual directions. We discuss four of them here.

Dialysis filter to combat cytokine storm

When the human body is attacked by a pathogen, it automatically defends itself. The immune system releases so-called cytokines to coordinate its defense. These are proteins with multiple functions: they act as messengers within the immune system, instructing the cells of the body to defend themselves against the viruses, and they increase the blood flow, which in turn leads to fever and inflammatory reactions in the body.

But the immune system can also overshoot the mark, at which point the dreaded cytokine storm kicks in – the body's own defense mechanism begins to damage the organs. The walls of the blood vessels become permeable, fluid leaks from the blood into the surrounding tissue, the circulatory system fails, and various organs stop working properly. In a severe case of Covid-19, the lungs are especially vulnerable, and the patient dies of ARDS (Acute Respiratory Distress Syndrome). We described this process in some detail in our Keynote 14 (Are you prepared for your personal battle).

Scientists are trying to curb the cytokine storm. The usual approach is via medication. But kidney specialists at the Medical College of Georgia and Augusta University had a different idea: Why not just mechanically extract the cytokines from the patient's blood?

At their university hospital, they had treated Covid-19 patients who required dialysis due to kidney failure. Dialysis involves a machine performing the function of the kidneys by filtering the patient's blood through a semi-permeable membrane. The kidney specialists speculated as to whether dialysis might be brought in at an even earlier stage of treatment.

They contacted Baxter International, the manufacturer of the dialysis machines, and established that the Oxiris filter is able to absorb bacterial toxins and cytokines from the blood like a sponge. This particular filter has been used in Europe and Asia for more than ten years.

The Medical College of Georgia and Augusta University team set about purifying the blood of Covid-19 patients with the Oxiris filter as soon as respiratory distress symptoms manifested themselves: "If we start this early on in the course of the disease, our expectation is that patients will have a better chance of survival. They will be less vulnerable to organ damage, as well as less susceptible to blood clotting, ARDS and kidney failure."

They are currently monitoring and recording disease progression. Baxter received emergency approval from the U.S. Food and Drug Administration (FDA) at the end of April for the use of the Oxiris filter to treat Covid-19 patients. Drs. Mohammed and Padala at the Medical College are planning a clinical study that could prove the effectiveness of the filter.

Another candidate in the battle against Covid-19: The human placenta

Admittedly, it sounds slightly bizarre, but scientists believe they may have found a possible weapon to use against Covid-19 – in the human placenta. The placenta is rich in stem cells. These remarkable cells are capable of being transformed into many different types of body cells.

A team led by Thomas Birch and Ravit Barkana at the Holy Name Medical Center in Teaneck, New Jersey, believe that stem cells not only calm the immune system down but also reinforce it in the fight against the virus. From previous research, it is known that placental stem cells can regulate the immune system.

Two biotech companies are currently trialing an experimental stem cell therapy on Covid-19 patients: The Israeli biotech company Pluristem Therapeutics has already treated six seriously ill Covid-19 patients with it.

And the U.S. company Celularity has received the green light from the American FDA to test its CYNK-001 cells on Covid-19 patients. Celularity has generated "natural killer" cells from placental stem cells and hopes that these cells will destroy virus-infected cells in the body.

A third new possibility: Artificial antibodies

The human immune system is a well-organized army of B-cells and T-cells. T-cells take the fight directly to the pathogens, while B-cells do this by means of antibodies, i.e. proteins that attach themselves to the invaders and neutralize them.

People who have survived a Covid-19 infection have these antibodies in their blood. Medical researchers see possibilities here. At the height of the epidemic in China, Chinese doctors collected blood from convalescent donors and transfused their plasma into Covid-19 patients who were at an earlier stage of the disease. The results were encouraging. Scientists led by Arturo Casadevall at Johns Hopkins University are currently trialing their own plasma therapy on Covid-19 patients.

As elegant and simple as the method may sound, it has its weaknesses. Blood plasma contains many different antibodies, and the concentration in a plasma transfusion of the antibody that specifically targets the coronavirus might be too low to have a sufficient effect in the recipient's body. In addition, there is not enough survivors' blood plasma available to treat Covid-19 patients at the current rate of infection, and certainly not for everyone who counts as high risk. In the USA, various hospitals and National Health Services are already calling for Covid-19 survivors to donate blood.

It would be better if the antibody that neutralizes the coronavirus could be identified and produced artificially in large quantities. Dozens of biotech companies are already working on this challenge, including major players such as Regeneron, AbCellera, GenScript, Astra-Zeneca, Berkeley Lights and VIR.

They are pursuing different strategies that include searching for the effective antibody in the blood of survivors and producing antibodies in animals (e.g. mice and llamas) by injecting them with the spike protein on the envelope of the coronavirus, and also modifying an existing artificial antibody.

The search for antibodies is problematic. For one thing, it takes several weeks before a patient who has recovered from Covid-19 has built up enough antibodies. And, as an article in the medical magazine Immunity reveals, the findings from samples obtained from 14 recovered Covid-19 patients show that these antibodies differ among themselves.

In order to find the antibodies that neutralize SARS-CoV-2, a research team at AbCellera have embarked on a kind of "fishing expedition" in the blood. They have taken the plasma of convalescents and used it to flush 200,000 tiny chambers that are so small they could fit on the surface of a credit card. The virus's spike protein is placed in these chambers as bait. The B-cells that take the bait are the ones the researchers are looking for. Once they have found such a B-cell, they can propagate it in bioreactors and produce larger amounts of so-called monoclonal antibodies – "monoclonal" because they all originate from a single cloned cell.

Monoclonal antibodies are already being used to treat a number of medical conditions, including various types of cancer and autoimmune diseases such as multiple sclerosis. They have also been successfully deployed against infectious diseases. For example, the American company Regeneron has developed a cocktail of three antibodies against the Ebola virus, which was very effective. Indeed, in a clinical trial, it came out ahead of two

other candidates, including the drug remdesivir, which has now ironically shown efficacy against Covid-19.

The hope is that a monoclonal antibody can be developed against novel coronavirus. Chinese researchers reported on 4th May in the journal Nature Communications that they had found such an antibody which they named 47D11. It attacks the spike protein and neutralizes both SARS-CoV-2 and the old SARS virus. However, the scientists have so far only demonstrated its effectiveness in cell cultures.

Whether the antibody is suitable will then have to be proven in clinical tests on humans, as is the case with any drug. That takes time. In the case of Ebola, where there was also epidemic pressure, Regeneron received approval after one year. This could be the crux of the matter, because it will take about that long before a vaccine is available, which could be cheaper and faster to produce than an antibody.

And there is another problem: the current production capacity for antibodies might not be sufficient to meet global demand. Carnley Norman, Vice-President of KBI Biopharma, a producer of antibodies, estimates that the largest plant currently in operation could only supply about one million people with antibodies. This means that many more such production facilities would have to be built.

Possibility number 4: Artificial ACE2 to fool the virus

As we have mentioned in previous Keynotes, viruses have to penetrate cells in order to multiply. Coronaviruses use their spike proteins to latch onto the ACE2 receptors on the surface of the cells. The cell then opens its gateways and becomes infected. ACE2 is mainly produced in cells found in the heart, lungs and kidneys.

However, the ACE2 receptor is also an enzyme and an important switch mechanism in the body for the regulation of blood pressure. People with high blood pressure therefore take so-called ACE inhibitors, drugs that block ACE2.

ACE inhibitors can cause the body to increase the number of ACE2 receptors on the cells. For this reason, we initially suspected that these drugs might be harmful to patients suffering from Covid-19. This fear has now been somewhat allayed by a clinical trial involving 8,900 Covid-19 patients. Nevertheless, we would still advise our customers to contact their Salvagene consultant if they intend to take ACE inhibitors.

An international team of scientists led by our colleague and fellow geneticist Josef Penninger at the Institute of Molecular Biotechnology in Vienna wants to use the entry portal ACE2 to fight the coronavirus. The plan is to have artificially generated ACE2 intercept the harmful viruses in the body before they can infect cells. Penninger has so far managed to prevent infection with SARS-CoV-2 viruses in cell cultures and on human organoids (organ-like cell structures that scientists have cultivated from stem cells).

APN01, an artificial ACE2 protein developed by the Austrian biotech company Apeiron Biologics, is currently being tested on 200 Covid-19 patients in Austria, Germany and Denmark. The results are expected in September.

Thank you for your interest. Look out for more news from the Salvagene SARS-CoV-2 Task Force.

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