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Opening up new possibilities to treat COVID-19 and cancer metastasis

Avalon GloboCare, a leading biotechnology company focusing on cell-based technology and therapeutics, is using its leading technology platforms to begin clinical trials of its potential COVID-19 therapy, a mucosal intranasal spray vaccination against SARS-CoV-2, and is developing drugs to combat cancer metastasis.

Avalon GloboCare, a US-based NASDAQ listed company (AVCO) is developing innovative cell-based therapeutics with key scientific partners, including Massachusetts Institute of Technology (MIT), the University of Natural Resources and Life Sciences (UNRLS) in Austria, Weill Cornell Medical Medicine in New York City, and the Lu Daopei Medical Group in China, which has the country's top-ranked hematology and bone marrow transplant program.

"As soon as the COVID-19 pandemic began, we focused on helping address the urgent needs for therapies and a vaccine strategy," said David Jin, CEO of Avalon GloboCare.

In early 2021, Avalon is planning a US-based first-in-human clinical trial of its AVA-Trap blood filtration system, designed to mitigate one the most severe effects of COVID-19—the surge in pro-inflammatory cytokines (a cytokine storm) that can cause multiple organ failure and contribute to death.

AVA-Trap combines two of Avalon's innovative core technologies: the QTY code and S-layer (Figs. 1 and 2). AVA-Trap technology utilizes cytokine receptor Fc-fusion proteins and antibody-like decoys that bind to the cytokines which are released by the immune system during a cytokine storm. "These proteins act like molecular sponges, soaking up excessive cytokines," Jin said.

The extracorporeal filtration system is also a potential treatment for cancer patients experiencing a cytokine storm induced by chimeric antigen receptor (CAR) T cell therapy, and other disorders that require rapid removal of cytokines from the body, including acute graft-versus-host disease (aGVHD).

The patient is hooked up to the AVA-Trap device, their blood circulates through the filtration system—an S-layer matrix attached to the cytokine receptor decoys—and the circulating cytokines are trapped by the decoy proteins. The uniform S-layer matrix allows for optimum conjugation with the QTY code-generated cytokine receptor decoys to achieve maximum binding and removal of the immune system-generated peptides.

While non-specific blood filtration systems exist, the AVA-Trap system uniquely traps and removes specific molecules of choice from the body. The innovative device can also serve as a diagnostic tool, isolating the cytokines or other molecules from a patient. "We can monitor the inflow and outflow cytokine concentration, titrate the cytokine status and optimize results for the patient," Jin said. "The key to this system is the combination of our two advanced technology platforms, the S-layer and the QTY code performing together."

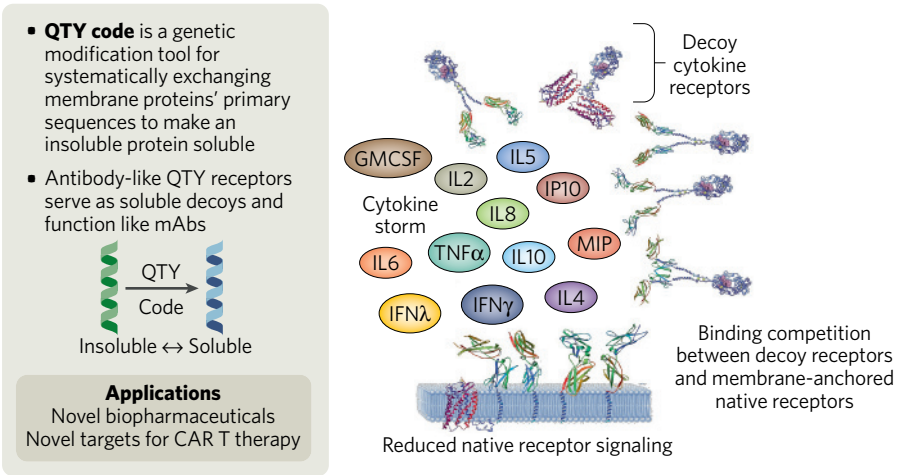

Fig. 1 | QTY code designed antibody-like decoy receptors. This technology, co-developed by Avalon GloboCare and Shuguang Zhang's laboratory at MIT utilizes a novel protein design strategy, called the QTY code. This technology platform can turn water insoluble transmembrane receptor proteins into water-soluble proteins, and fuse them with an Fc region of an IgG protein to form an antibody-like structure, enabling the use of these proteins in many clinical applications. The QTY code technology has been applied to Avalon's AVA-Trap blood filtering system, as well as to a novel methodology to re-engineer immune cells for cellular immunotherapy. GMCSF, granulocyte-macrophage colony-stimulating factor; IFN, interferon; IL, interleukin; IP10, Interferon gamma-induced protein 10; mAbs, monoclonal antibodies; MIP, macrophage inflammatory protein; TNF, tumor necrosis factor.

Avalon is also collaborating with researchers at the MIT to apply the novel QTY protein code technology to tackle cancer metastasis, which is responsible for the vast majority of cancer deaths. Avalon and MIT are applying the QTY code in order to design truncated versions of chemokine receptors that normally act to mobilize cancer cells, allowing them to travel to other organs through the chemokine signaling network. The decoy QTY-based receptors may act as a sink, attracting cancer cells and preventing them from spreading to other organs. Avalon and MIT researchers are also combining the QTY technology with the CRISPR-Cas9 gene editing system to re-program cell types that typically stimulate nearby cancer cells to spread, therefore preventing cancer metastasis.

Mucosal, intranasal COVID-19 vaccine

Avalon is also using its S-layer technology in an intranasal, spray vaccine candidate against SARS-CoV-2. The first-in-human clinical trials are planned for early 2021.

"This coronavirus is transmitted predominantly through droplets and airborne aerosols. Providing a first-line immune protection at the oropharynx, where the virus enters the body, is likely to be important," Jin said.

The S-layer nanoproteins can be induced to self-assemble into spherical, ordered particles that mimic the dimensions and structure of a pathogenic virus. These particles are not themselves infectious as the virus-mimic does not contain pathogenic viral components. The vaccine candidate is essentially an artificial viral envelope that resembles the SARS-CoV-2 virus surface structure. Layered on top is the SARS-CoV-2 specific protein antigen, the major surface protein of the coronavirus that facilitates viral entry into human cells.

"The S-layer protein-based vaccine is expected to decrease the severity of a SARS-CoV-2 infection, thus preventing severe forms of COVID-19, including severe respiratory inflammation and organ damage, while establishing immunity against the virus," Jin said.

The speed with which the scientific community has developed SARS-CoV-2 vaccine candidates is unprecedented, with phase 3 clinical trials of several injectable candidates well underway. A major question is how long immunity will last, Jin pointed out.

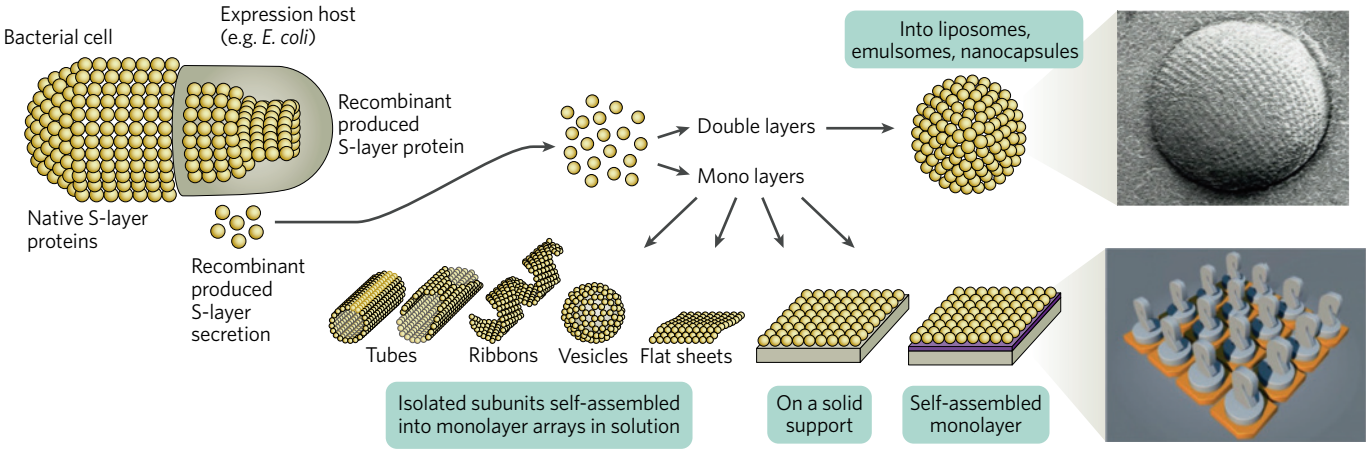

Fig. 2 | S-layer technology. Avalon has partnered with Uwe B. Sleytr, a pioneer in nanotechnology and an expert on S-layer technology, at Vienna's UNRLS. S-layer proteins are naturally occurring proteins on the surface of many bacteria, and the technology is based on the repetitive protein structures that make up the outer surface of microbial cells. S-layer protein materials can be induced to self-assemble into spherical 3D, crystal structures around a passive, scaffold material, resulting in a particle that mimics the dimensions and structure of a pathogenic virus. A cartoon illustration of the self-assembled S-layer (orange) fusion proteins carrying a functional domain (knights) in a defined position and orientation is shown (bottom right) and a transmission electron microscopy image of a freeze-etched liposome covered with a crystalline, highly ordered S-layer is shown (top right). Diameter of the S-layer coated liposome is in the 200 micrometer (micron/μm) range.

"We see our vaccine candidate as a complement to any injectable vaccines in clinical trials, because it could provide first-line immune protection at the virus entrance site," he added. "We're very excited about our intranasal vaccine candidate. If immunity generated by injectable vaccines has finite durability and will require boosting, that will be difficult to achieve using injectable vaccine boosters. If our nasal spray vaccine is effective, it could confer immunity at the level of the oral mucosa, which would be a great advantage and very convenient."

The spray vaccine has the dual advantages of ease of manufacturing and delivery. There is also a public health advantage. For rural communities and less developed countries, the ability to more easily administer a spray vaccine, as opposed to an injectable vaccine, could facilitate wider distribution.

The S-layer vaccine technology also enables conjugation to different types of viral antigens on the vaccine. With the potential of a 'twindemic' of influenza and SARS-CoV-2 during fall and winter, Avalon is also planning to conjugate the S-layer matrix with an antigenic signature from both SARS-CoV-2 and the influenza virus for one spray that, if proven effective, would provide protective immunity against both viruses. The S-layer can also be quickly adapted to modify the viral antigen peptide if a novel viral strain is isolated, as influenza strains mutate seasonally.

The partnership's goal is to utilize S-layer technology to expand into additional vaccine programs for other respiratory infections including respiratory syncytial virus (RSV). Avalon is also exploring other practical uses of S-layer technology including targeted drug delivery, diagnostic devices and therapeutic applications.

Allogeneic mesenchymal stromal cell therapy

Avalon will begin clinical trials in the US and China in Q4 2020 and Q1 2021 with CB-MSC-1, an innovative, allogeneic mesenchymal stromal cell (MSC) therapy candidate derived from human cord blood. MSCs possess unique anti-inflammatory and immunomodulatory activities, with the ability to suppress T cell proliferation, cytokine secretion and regulate the balance of antibody-based and cell-based immune responses. These cells can also dampen the abnormal release of antibodies from B cells and cytokines from natural killer cells.

Avalon has completed pre-clinical studies and the standardized process development for CB-MSC-1 and will run first-in-human clinical trials for acute respiratory distress syndrome (ARDS) associated with severe respiratory infections including in COVID-19 patients, and patients who develop aGVHD following bone marrow transplantation.

Avalon is also planning a trial for patients with multi-system inflammatory syndrome, a serious complication thought to be associated with COVID-19 in children. Leveraging the company's scientific and clinical expertise in cellular therapy and stem cell-derived exosome (ACTEX) technology, Avalon is also planning a clinical trial of ACTEX-M, the clinical-grade exosomes derived from CB-MSC-1 as a candidate topical treatment for cutaneous aGVHD.

"If our clinical trials are successful, AVA-Trap and CB-MSC-1 could both make a difference for COVID-19 patients—AVA-Trap for those with a cytokine storm and MSC therapies for individuals who develop ARDS," said Jin.

These studies are in conjunction with Avalon's research partners at Weill Cornell Medicine in New York City and the Lu Daopei Medical Group in Hebei Province, China. The company's major clinical base for aGVHD is at Lu Daopei Medical Group, one of the world's largest bone marrow transplant centers. "aGVHD is a complication of the transplant process which usually affects the liver, skin and gut. Right now there's no good therapeutic approach for aGVHD," said Jin.

"Steroids and immune-suppressive therapeutic agents are used in the organ transplant setting, but these are associated with many side effects and high toxicity, which is why we are focusing our cord blood-derived MSC program for these patients," Jin explained.

Third generation CAR T cell therapy

Avalon's clinical pipeline also includes AVA-001, a third-generation CAR T cell therapy which involves the 4-1BB (or CD28) co-stimulation signaling pathway, and is designed to confer a more effective capacity for cancer cell-killing compared to older generation CAR T cell therapies.

In the first quarter of 2020, Avalon successfully completed a phase 1 first-in-human clinical study of AVA-001 in China for the treatment of relapsed/refractory B cell acute lymphoblastic leukemia (R/R B-ALL). 90% of patients achieved complete remission with one dose and within one month of treatment, and then proceeded to a curative-intent allogeneic bone marrow transplant.

Accompanying laboratory testing results in the trial revealed evidence of enhancement in CAR T cell persistence and protection against CAR T cell exhaustion. Patients also retained a high level of engineered CAR T cells, and experienced low levels of toxicity.

Avalon is now advancing AVA-001 for R/R B-ALL to the next phase of clinical development and is also expanding the current clinical trial to recruit patients with R/R Non-Hodgkin lymphoma (NHL). This clinical paradigm of bridging CAR T cell therapy to bone marrow transplant is poised to provide a new therapeutic horizon with curative potential for patients with R/R B-ALL, NHL and other hematologic malignancies.

"Currently, CAR T cell therapies are for hematologic malignancies including leukemias and lymphomas," Jin said. "Refractory and relapse patients have already exhausted most of their therapeutic options. With the development of next generation CAR T cell therapies, we have an opportunity to bring down patients' disease burden and follow with a potentially curative transplant. Based on our data to date, our third-generation CAR T cell approach is relatively safe and effective. This gives us tremendous confidence in bringing our cell therapy to patients."

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