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The Intersection of PHYSICS AND BIOLOGY

Daniel O'Connor, President and CEO of OncoSec, talks about his company's efforts to develop new technologies to stimulate the body's immune system to target and attack cancer.


Daniel O'Connor

It is estimated that there are 1.6 million new cases of solid tumor cancers in the United States alone, presenting one of the largest challenges to oncologists. Solid tumor cancers bypass or hide from the immune system by engaging an immune checkpoint called PD-1, which cancers can exploit to escape from cancer-fighting T-cells. Furthermore, anti-PD-1 checkpoint inhibitors are only effective in an estimated 30% of cancer patients.

OncoSec aims to address the other 70% of patients. The company is developing immunotherapy cancer treatments using its plasmid DNA delivery platform, which has the potential to boost the immune response against tumors and cancerous lesions. This novel method of delivering the potent immunomodulatory cytokine interleukin 12 (IL-12) directly into the tumor is followed with electroporation gene delivery and is designed to produce a controlled, localized expression of IL-12 in the tumor microenvironment, enabling the immune system to target and attack tumors throughout the body.

Electroporation involves the use of electrical pulses to increase the permeability of the cell membrane, permitting genetically engineered DNA to be injected directly into a tumor or tumors. The cell membrane reseals and the electroporated cells manufacture the immune stimulatory proteins according to the specifications engineered into the DNA-based agent. "Our technology intersects physics and biology," says Daniel O'Connor, president and CEO of OncoSec. "Running energy into the membrane of a cell causes micropores to form for a brief moment, and those micropores close when the energy stops. That split second of energy presents an opportunity for a DNA plasmid to transect or move from outside of the cell to inside the cell. The cell then produces the proteins that were put on to the DNA plasmid."

In addition to being efficient, Mr. O'Connor says electroporation is nontoxic and it preserves the integrity of the cell, which allows the cell to receive the plasmid.

The company's most advanced program, TAVO (tavokinogene telseplasmid), is a 100-patient study for stage III-IV melanoma, involving patients who failed prior checkpoint therapy. Results from recently completed clinical studies of TAVO have demonstrated a local immune response, and subsequently, a systemic effect as either a monotherapy or a combination treatment approach. Data from OncoSec's Phase II melanoma program provides preliminary evidence of anti-tumor activity with abscopal effect.

Data indicates that local delivery and expression of TAVO promotes tumor immunogenicity and increases tumor-infiltrating lymphocytes (TILs). As a pro-inflammatory cytokine, IL-12 can promote the recruitment of T-cells to the tumor. By driving T-cells or TILs into the tumor microenvironment, TAVO may enhance response to anti-PD-1 and convert anti-PD-1 non-responders to responders.

Mr. O'Connor says IL-12 can change the ability of tumors to suppress the immune response. "The process involves up-regulating interfering gammas, an element that is able to deliver immunologically relevant elements into immunologically relevant places," he says. "Tumors are cold and immunosuppressive, so the idea is to promote a pro-inflammatory response. This dovetails extremely well with checkpoint inhibitors; when checkpoint inhibitors are working, it's generally because the tumor microenvironment is devoid of white blood cells, and IL-12 can change the tumor biology."

OncoSec is conducting Phase II trials of TAVO in combination with Merck's Keytruda, a PD-1 checkpoint inhibitor, in patients with heavily pretreated, metastatic, chemotherapy refractory triple negative breast cancer. Interim data from the study showed about 50% of evaluated patients experienced a 20% or greater tumor reduction. Triple negative breast cancer is an aggressive type of cancer that characteristically has a high recurrence rate within the first five years after diagnosis.

The two therapies are important for patients who have been nonresponders to checkpoint inhibitors such as Keytruda, Mr. O'Connor says. "Keytruda still does its job — blocking the antibody that interferes with the immunosuppressive mechanism, in essence taking the so-called brakes off the immune response," he says. "When checkpoint therapies fail patients, it generally is because they have tumors that are immunologically not receptive to the treatment. And this is usually determined by the level of white blood cells and infiltrating lymphocytes that are present before treatment with the checkpoint."

Additionally, the company recently began a trial of TAVO and Keytruda in patients with unresectable squamous cell carcinoma head and neck (SCCHN) cancer.

OncoSec also has entered into a collaboration with Dana-Farber Cancer Institute and The Marasco Laboratory to develop CAR T-cell therapies for triple-negative breast cancer and other solid tumor cancers. CAR T-cell therapies have revolutionized hematologic cancer treatment. But solid tumors, which account for 90% of cancer cases, present a unique set of challenges.

The company plans to study the combination of TAVO (IL-12) and CAR T-cell therapy to see if they can be furthered enhanced for the treatment of solid tumors. This study capitalizes on findings from a 2017 plot study of TAVO in head and neck cancer patients, which demonstrated impressive clinical and biological results, including evidence of synergy between TAVO and PD-1 antibodies in the disease.

In addition to TAVO, OncoSec is identifying and developing new DNA-encoded therapeutic candidates and tumor indications for use with its new Visceral Lesion Applicator (VLA), to target deep visceral lesions, such as liver, lung, or pancreatic lesions. This proprietary gene delivery system has demonstrated the potential to become a foundational technology in the treatment of earlier-stage, localized malignancies. PV