OncoSec Medical Incorporated

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ONCOSEC™

Creating an arsenal of immunotherapies to fight cancer

OncoSec's platform, ImmunoPulse, delivers immune modulators directly into tumors to activate an orchestrated anti-tumor immune response

In addition to defending against infection, the immune system can identify and destroy tumor cells, but to do so it must fight a cloak-and-dagger battle with tumors capable of both evading detection and disarming immune effector cells. When tumors succeed, they create an immunosuppressive local environment to support their continued growth. Recent clinical success using immune checkpoint inhibitors (e.g., ipilimumab, pembrolizumab and nivolumab) has shown that reversing immunosuppression can unleash a powerful antitumor response and improve outcomes in numerous cancer types, including melanoma, renal cell carcinoma and non–small cell lung cancer.

Immune checkpoints are just one of the targets in the immune system that can be subverted by tumor cells. In fact, in clinical studies, treatment of solid tumors with a checkpoint inhibitor failed to trigger an effective immune response in most tumor types in the majority of subjects. Closer examination of tumors that respond to immune checkpoint inhibitors has revealed programmed cell death 1 (PD1)-positive and $CD8^+$ tumor-infiltrating lymphocytes (TILs) at the invasive margin of the tumor, close to programmed cell death ligand 1–positive tumor and myeloid cells. In melanoma, TILs are notably absent in patients who do not respond to anti-PD1 therapies, which suggests that the tumors in such patients lack adequate immunogenicity. For patients with these less immunogenic tumors, additional monotherapies or combination immunotherapies are needed to overcome this barrier and trigger tumor rejection.

Scientists at OncoSec have developed a platform technology, ImmunoPulse, to create new treatments to meet the need for effective immunotherapies against tumors that lack TILs. The technology uses electroporation to introduce DNA encoding immune modulators, such as cytokines and antibodies, directly into the tumor microenvironment, with the aim of reversing immune suppression and provoking an antitumor response. To this end, engineered DNA encoding the protein or proteins of interest is injected into the tumor (**Fig. 1a**), and then the needle applicator delivers short electrical pulses to briefly open cell membranes, allowing the engineered DNA to enter the cell (**Fig. 1b**). After DNA uptake, the cell membrane closes (**Fig. 1c**), and the cells express the immune modulators encoded by the DNA.

According to Robert Pierce, OncoSec CSO, ImmunoPulse offers distinct advantages as a method for delivering immune modulators to tumors.

- It avoids constraints imposed on DNA length by viral packaging, allowing combination immunotherapy with multiple genes in a single DNA treatment.
- It has shorter timelines to hypothesis testing and proof of concept.
- It has a decreased risk of neutralizing antibody responses.
- It lowers the cost of goods.

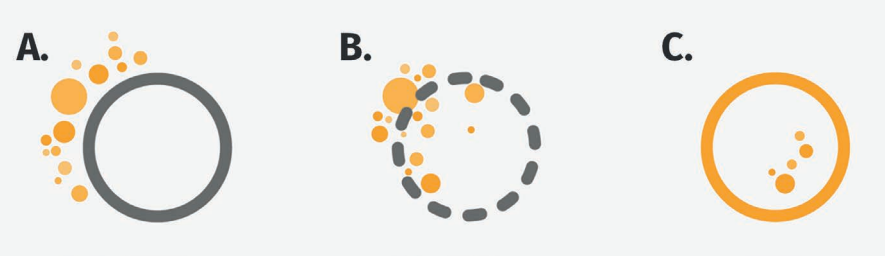

Figure 1: How ImmunoPulse works. (**a**) Genetically engineered DNA (yellow dots), designed to code for immune-stimulatory proteins, is administered or injected directly into the tumor(s) (gray circle). (**b**) The needle applicator supplies a sequence of short-duration electrical pulses to the tumor(s). This increases the permeability of the cell membrane and facilitates uptake of the DNA-based agent(s). (**c**) The cell membrane reseals with the DNA inside, and the electroporated cells manufacture the protein according to the specifications engineered into the DNA-based agent. Expression of immunomodulatory cytokines, antibodies and other proteins can be expressed *in situ*, leading to local and systemic effects.

OncoSec's first intratumoral cancer immunotherapy to enter the clinic, ImmunoPulse IL-12, is DNA engineered to produce IL-12, a cytokine that was selected, according to Pierce, because it is the "master switch needed to lock in a type 1 helper T cell response." ImmunoPulse IL-12 is being tested clinically in metastatic melanoma and other solid tumors. This includes a combination study with ImmunoPulse IL-12 and Merck's approved PD1 antibody, pembrolizumab, conducted in collaboration with Merck and the University of California, San Francisco. This trial is designed to identify patients with low TIL levels, as indicated by flow cytometric analysis, and will include patients who failed on prior immunotherapy. Post-treatment biopsies are also being assayed to measure the impact of the combination therapy on TIL levels.

ImmunoPulse IL-12 has already shown promise as a monotherapy for metastatic melanoma. Of 29 patients in the phase 2 trial, 14% made a complete response, 48% showed controlled disease and 50% experienced regression in at least one untreated lesion.

In September OncoSec also announced positive results in a phase 2 study of ImmunoPulse IL-12 in Merkel cell carcinoma, a rare and aggressive skin cancer. According to Shailender Bhatia, assistant professor of medicine at the University of Washington School of Medicine and principal investigator of the trial, "Our findings support the hypothesis that intratumoral IL-12 DNA with electroporation promotes tumor immunogenicity." Specifically, 79% of patients (11 out of 14) showed an increase in IL-12 protein levels in tumor biopsy samples indicating that ImmunoPulse IL-12 led to successful DNA transfection and sustained protein expression within the tumor microenvironment. The therapy was also well tolerated, with no treatment-related adverse events above grade 2 and no treatment-related serious adverse events.

Clinical data to date has laid the groundwork for OncoSec to seek new immune-targeting agents, explore additional tumor indications and evaluate combination-based immunotherapy, both independently and with collaborators. Moving beyond cutaneous tumors, OncoSec has also initiated a study of the pharmacodynamics of ImmunoPulse IL-12 in triple-negative breast cancer. Current preclinical projects include a collaboration with Heat Biologics to investigate the potential of combining its new heat shock protein GP96–based ImPACT therapeutic vaccine with ImmunoPulse to expose and vaccinate patients against critical, patient-specific neoantigens. With its platform technology, OncoSec hopes to continue to expand the arsenal of immunotherapies available to fight cancer.

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