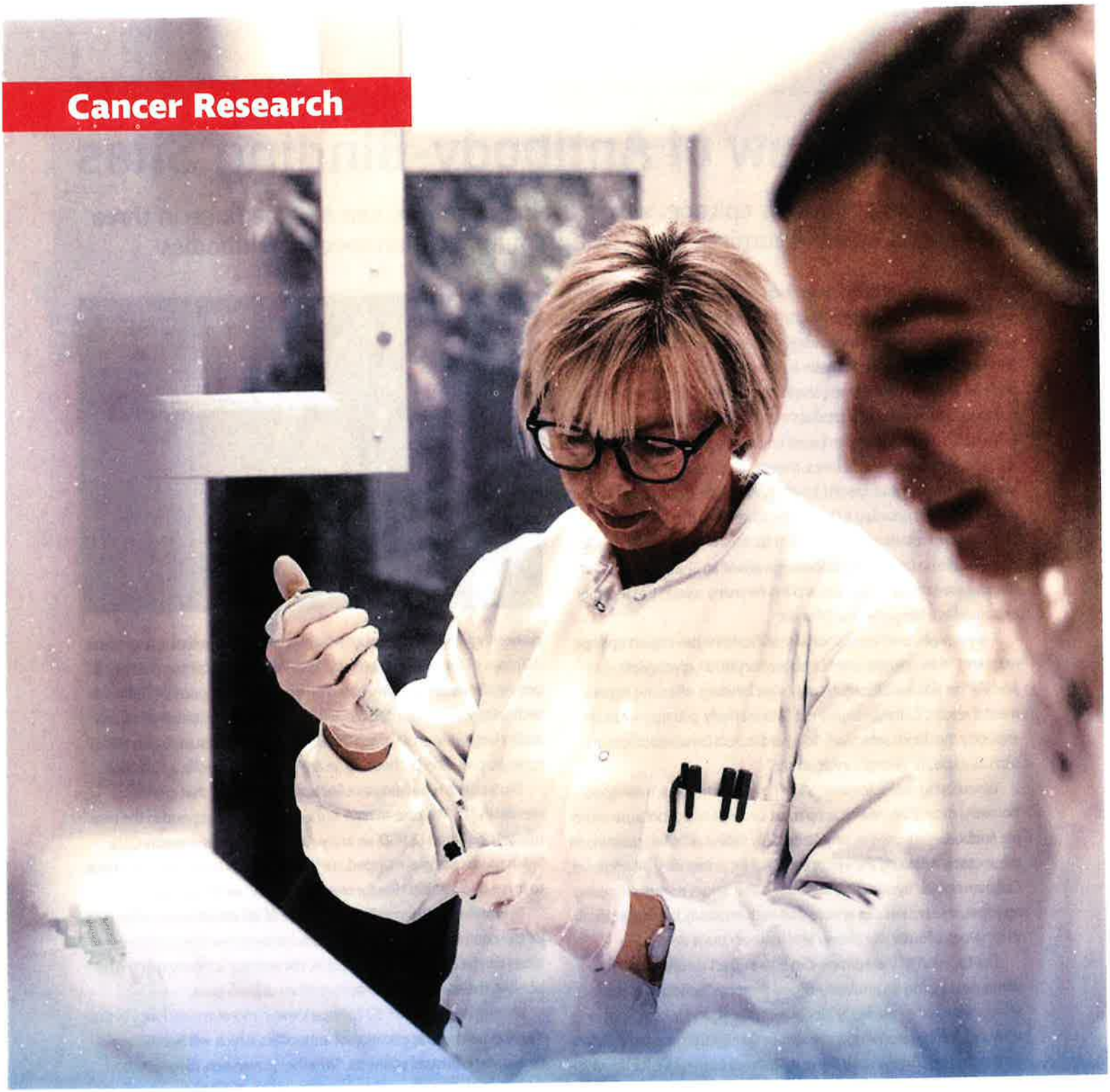


Cancer Vaccines
Improve Their Aim

Converging computational and laboratory technologies are helping anti-cancer immune responses hit their target more effectively

By Caroline Seydel

Cancer vaccines have been a tantalizing idea for decades, but the vast complexity of the human immune system has posed significant challenges. Now, technological advances like rapid DNA sequencing, lymph node targeting, and AI-informed antigen selection are enabling the creation of precision vaccines that target cancers effectively while minimizing harmful side effects.

Combating cancer's immunosuppressive effects

One early cancer vaccine, developed in the late 1970s, was made from pooled human colorectal tumor tissue, fractionated and screened for immunogenicity. Back then, it was no simple matter to identify the antigen that triggered the immune response, but clinical trials revealed that the vaccine could successfully induce both a T-cell response and antibody production. "What got us excited was that antibody responses–IgG responses–against the vaccine correlated with better outcomes," says Philip Arlen, MD, CEO of **Precision Biologics**. Based on that observation, Precision screened for tumor-targeting antibodies that could be manufactured as therapy for patients.

Once they had identified a lead candidate antibody, which they named NEO-201, the next step was to identify its target antigen. This turned out to be a sugar group, called a core 1 O-glycan, that is specific to glycosylated proteins expressed by cancer cells, meaning the antibody won't react to healthy tissues. There is an important exception, however: this particular O-glycan is expressed by regulatory T cells and granulocytic myeloid-derived suppressor cells (GMDSCs), two types of cells that suppress the immune response.

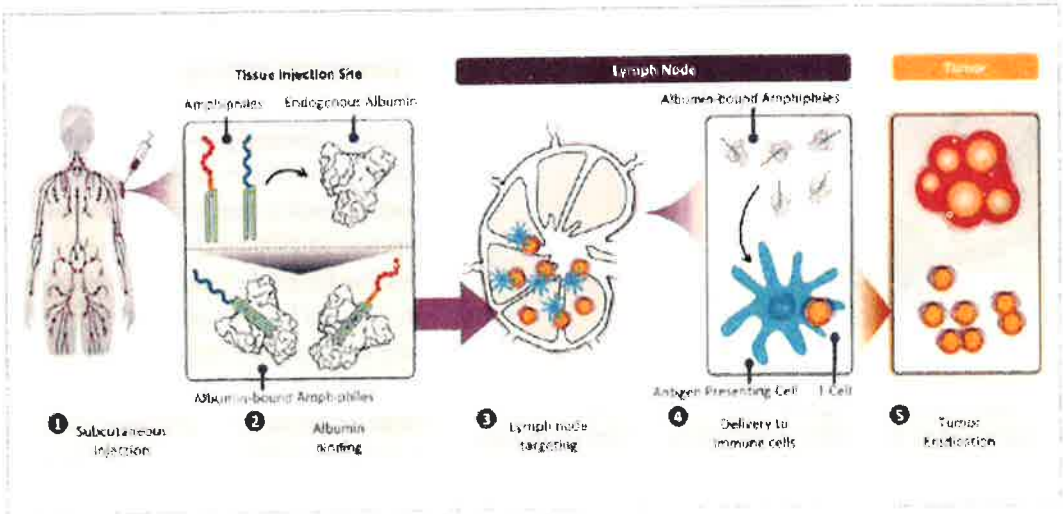
Treatment with NEO-201 reduced the numbers of these immune-regulating cells, Arlen says. "We realized this would be a really interesting drug to combine with T-cell immunotherapy." Precision is currently running a Phase II study (NCT03476681) combining NEO-201 with the immune checkpoint inhibitor (ICI) pembrolizumab for patients whose disease has progressed after prior ICI treatment. Accumulation of immune suppressor cells in the tumor microenvironment inhibits the activity of ICIs, so NEO-201 could potentially restore the efficacy of the ICIs.

"I think this is where oncology is heading," says Arlen. "We're looking at ways of combining NEO-201 with other therapies, either as a naked antibody or creating next-generation molecules or drugs from NEO-201, including CAR T/CAR NK cells, T-cell/NK-cell engagers, bispecific antibodies, and antibody-drug conjugates."

Targeting the lymph nodes

A lymph node-targeting vaccine from **Elicio Therapeutics** has delivered promising early results in a Phase I trial (NCT04853017) of patients with

Left. Evaxion uses an AI platform to select 10 candidate neoantigens from a patient's cancer that are most likely to generate a strong T-cell response, and use those antigens to develop a personalized vaccine. Evaxion's vaccines are designed to work synergistically with checkpoint inhibitors, but could eventually be used as monotherapy.



Elicio's amphiphiles allow the immunostimulatory drug to hitch a ride on albumin, which travels to the lymph nodes. Once inside the lymph node, the amphiphile lets go of albumin, allowing the drug to be taken up by antigen-presenting cells (APC), which stimulate a tumor-targeting T-cell response.

KRAS-mutated pancreatic cancer, tripling the expected median relapse-free survival from 5 to 16 months. By targeting the lymph nodes, the vaccine improves the T-cells' cancer-killing ability while also reducing off-target inflammation, explains Christopher Haqq, MD, PhD, chief medical officer at Elicio.

Elicio's strategy requires a specially designed amphiphile molecule that simultaneously binds to the immunostimulatory drug and the protein albumin, which travels to the lymph nodes. Importantly, once inside the lymph node, the amphiphile releases the drug so that it can be taken up by immune cells.

The company's lead candidate, ELI-002, targets KRAS mutations, found in some 25% of all solid tumors including 88% of pancreatic ductal adenocarcinomas. The drug incorporates antigens corresponding to seven different KRAS mutations, plus an adjuvant that stimulates TLR-9, an immune system activator typically triggered by bacterial infections. Sending the vaccine directly to the lymph nodes avoids indiscriminate immune activation.

"Unlike the soluble format, which can go anywhere in the body and cause inflammatory effects, all of the effects of our drug are kept in the lymph node," Haqq explains.

Data from 39 patients with advanced pancreatic or colorectal cancer shows that Elicio's vaccine induced 100-fold increases in tumor-specific T cells without any serious safety concerns. Elicio's off-the-shelf formulation trades personalization for speed–an advantage for patients with fast-progressing disease–but even so, it appears that the anti-KRAS vaccine also boosts T-cell responses to other tumor antigens. Among patients in the Phase I trial, 70% had a measurable increase in T cells targeting tumor antigens not included in the vaccine. "That's encouraging," Haqq says. "The anti-KRAS T cells are able to attract other T cells to join them to make an attack on the tumor, and that might lead to really great long-term outcomes." A randomized Phase II study is currently underway.

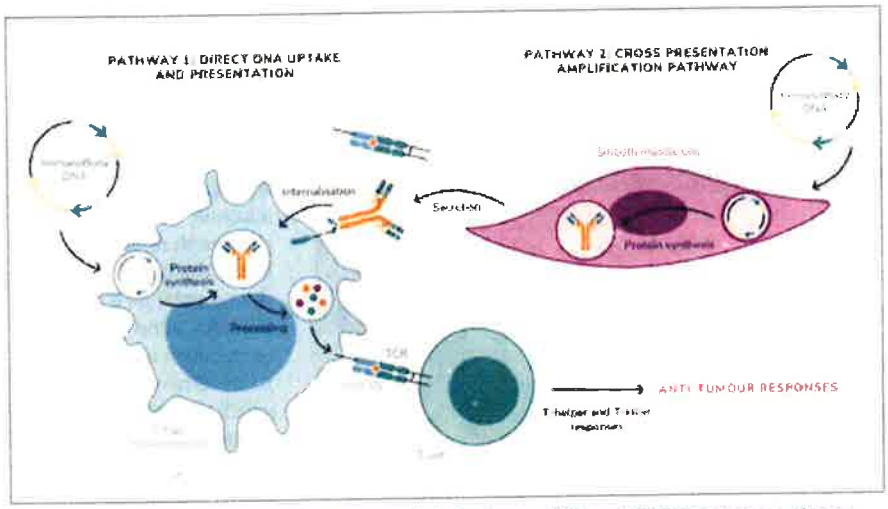
Off-the-shelf vaccines can be fast and effective

To design their melanoma vaccine, Scancell looked for clues in the T cells of patients who had spontaneously recovered from melanoma. They identified specific epitopes from two proteins, gp100 and TRP-2, both essential for melanin production and therefore present in all pigment-producing melanomas. The SCIB1 vaccine consists of a DNA plasmid encoding two CD8 epitopes and two CD4 epitopes drawn from these proteins and built into an antibody framework. In clinical trials, both alone and combined with other immunotherapies, SCIB1 has performed better than standard of care.

In a Phase I study, 89% of patients with advanced melanoma survived for 5 years after surgery, compared with an expected 50% for checkpoint inhibitors. In the Phase II study (NCT04079166), currently ongoing, patients with unresectable melanoma received SCIB1 plus ipilimumab and nivolumab. After 25 weeks, 80% of the first 25 patients have seen their tumors either shrink or remain stable. In five patients, the cancer disappeared completely.

"We're seeing very early signs of a big benefit on top of standard of care, and we're not seeing any safety issues," says Phil L'Huillier, PhD, CEO of Scancell.

Scancell's other vaccine platform targets post-translational modifications. The vaccine candidate Modi-1 targets a modification called citrullination; it consists of three citrullinated tumor-associated peptides that stimulate a CD4+ T-cell response. A Phase IIa trial (NCT05329532) is currently underway testing Modi-1 in patients with HPV-negative head and neck cancer or renal cancer. Early results have been promising, with an overall response rate of 43% in patients with head and neck cancer, compared to an expected 13-19% for checkpoint inhibitors. Results for the renal cancer patients are expected later this year. "It's very early days, but it's a very novel approach, and head and neck cancer has been pretty tough for checkpoint inhibitors to see any real benefit," L'Huillier says. "So I'm really hopeful in that setting."



The Immunobody platform from Scancell includes gp100 and TRP-2 epitopes, chosen because they are known to be expressed by the T cells of melanoma patients that have spontaneously regressed. The Immunobody is taken up by antigen-presenting cells which then express the epitopes, stimulating killer T cells to target the cancer cells.

Harnessing AI for personalized antigen selection

Evaxion Biotech, which specializes in AI platforms for antigen discovery, has reported one-year interim data from a Phase II trial (NCT05309421) underway for its peptide-based personalized cancer vaccine candidate, EVX-01. Patients with metastatic melanoma received the vaccine together with pembrolizumab, an anti-PD-1 immunotherapy. Among the 16 patients in the study, there has been a 69% overall response rate. "The data is very promising," says Birgitte Rønø, PhD, chief scientific officer at Evaxion. "We definitely see that there is an improvement compared to pembrolizumab monotherapy."

To create the personalized vaccine, Evaxion collects two genome sequences, one taken from the tumor biopsy and a second one from the patient's blood sample. The AI-Immunology™ platform compares these sequences and identifies the most promising targetable neoantigens in the patient's cancer. Then, 10 neoantigens are selected to be synthesized as peptides, each 27 amino acids in length, for the vaccine. "We continue to optimize the time frame, but from biopsy to therapy, we've been able to produce the vaccines within seven weeks," says Rønø.

Rather than packing more neoantigens into each vaccine, Rønø says, Evaxion prioritizes quality over quantity. Data from the Phase II trial has shown that 79% of the neoantigens selected as targets triggered an immune reaction in patients. "That is a very high number compared to what some of our competitors have demonstrated," she says. Evaxion has trained its AI platform on both publicly available and proprietary datasets that include all different HLA haplotypes, enabling a more precise antigen selection process for a wide variety of patients.

So far, adding EVX-01 to pembrolizumab has not increased the number or severity of adverse events reported. "It's a therapy that is extremely safe, and we don't see why it shouldn't be globally applicable for other cancers," says Rønø.

For targeting cancer antigens, more is better

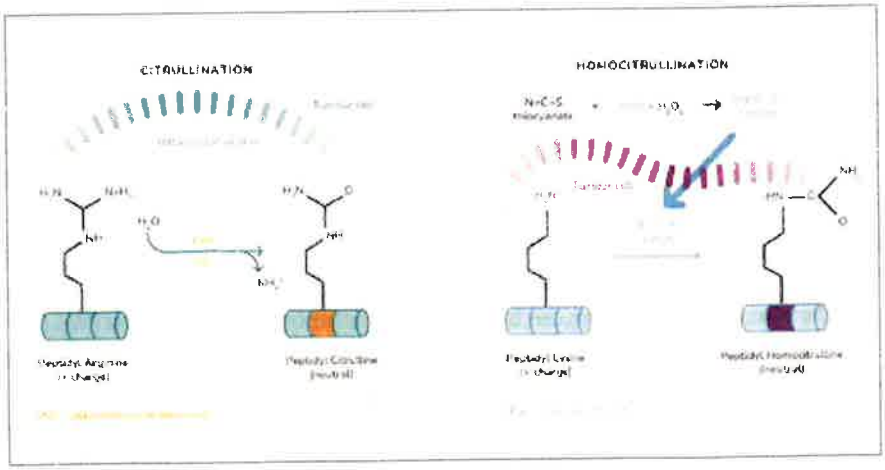
Cancer cells can evolve quickly to evade the immune system, meaning that T cells hunting for a single cancer-associated antigen can become ineffective if the cancer stops making that antigen.

"More is better when it comes to neoantigen targeting," says Niranjan Sardesai, PhD, CEO of **Geneos Therapeutics**. "Targeting more neoantigens gives you multiple shots on the cancer and makes it difficult for the cancer to evade the immune system."

Geneos incorporates up to 40 antigens into their personalized therapeutic cancer vaccines, or PTCVs. Targetable neoantigens are identified by comparing gene expression between the tumor biopsy and the patient's normal blood sample. The PTCV includes a plasmid encoding a selection of neoantigens plus a second plasmid encoding IL-12, a T cell-stimulating cytokine. Right now, the entire preparation process end-to-end takes five weeks, Sardesai says. The end product is truly individualized: so far, no two patients' vaccines have had more than one antigen in common.

In a Phase I/II clinical study of 36 patients with metastatic liver cancer that had returned after treatment with tyrosine kinase inhibitor therapy, participants received pembrolizumab plus a PCTV from Geneos. The findings were published in *Nature Medicine* in a paper entitled, "Personalized neoantigen vaccine and pembrolizumab in advanced hepatocellular carcinoma: a phase 1/2 trial." In three patients, the treatment eliminated the cancer completely, and a fourth patient's tumor was reduced enough that it could be surgically removed. "We're the only group that has shown meaningful clinical efficacy in an advanced, metastatic, unresectable cancer setting," says Sardesai. "We are seeing some remarkably durable responses in our patients."

The platform is tumor-agnostic, Sardesai says, so Geneos is looking at applying their vaccines to a variety of cancer types–particularly those with low tumor mutational burden, such as prostate, ovarian, and glioblastoma, which have traditionally been unresponsive to immunotherapy. "We can make the most impact in these tumors," says Sardesai. "We look at that as a wide-open space for developing the next generation of products." GEN



The Moditope platform targets cancer-specific post-translational modifications found on neoantigens, specifically citrullination and homocitrullination. In early results, Scancell's Modi-1 vaccine has shown promising results as monotherapy in cancers traditionally resistant to checkpoint inhibitors. Scancell