The 'immuno revolution': Turning up the heat on resistant tumors

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A promising class of drugs known as CD40 monoclonal antibodies could be the spark needed to light the fire in the immune system of patients who don't respond to the newer cancer immunotherapies.

Robert H. Vonderheide, MD, DPhil, director of the Abramson Cancer Center at the University of Pennsylvania and an internationally renowned cancer immunotherapy expert, makes the case for the drugs in a new perspective piece published this week in *Cancer Cell*, as part of a series in the issue focusing on the next phase of the evolving field of cancer immunotherapy.

"The 'immuno revolution' is upon us: We're battling cancers like never before by tapping into the power of the immune system with checkpoint inhibitors and personalized cellular therapies that have elicited stellar responses in patients," Vonderheide said. "But there is a bittersweet quality to these successes: many patients do not respond or quickly relapse after an initial response."

The PD-1 antibody pembrolizumab, for example, is approved for use as a first-line therapy for patients with metastatic non-small cell lung cancer that overexpresses PD-L1, which cancer cells use to hide from the immune system, yet nearly 30 percent of patients don't respond to the therapy and another 25 percent have tumor progression at one year.

"To overcome the resistance in these patients, we need to go back to the beginning and prime the T cells before we jumpstart their immune system with other therapies to attack the cancer," Vonderheide said.

The CD40 antibodies activate antigen-presenting cells, such as dendritic or B cells, to prime tumor-specific T cell responses, effectively "pushing the gas" on the immune system to make it work harder. This "lead-in" therapy, which is being investigated in clinical trials around the world, including at Penn Medicine, has been shown to turn so-called "cold" tumors hiding from the body's defenses into "hot" ones by "priming" the T cells before other treatments.

Think of the body's immune response like an assembly line, with points A, B, C, D, and E, that kill the tumor at the end, Vonderheide said. For example, a T cell starts, it expands, it gets exhausted, and stops because of the PD-1 pathways. Checkpoint inhibitors take that brake off toward the end, so the T cells can then attack the tumor.

"We've been drugging the very last step," said Vonderheide, who serves as a principal investigator on several CD40 combination trials at Penn, including a national trial through the Parker Institute of Cancer Immunotherapy. "In many patients, however, that won't work because points A through E hasn't happened. You can give them a checkpoint inhibitor, but there are no T cells to take the brakes off."

"With the CD40 drugs, we're back at point A to prime the T cells in the body to continue on in the immune response," he added. "Once you get A going, you can potentially treat more patients."

CD40 agonists have moved successfully from preclinical studies, many of which have been conducted by Penn researchers, where they have demonstrated anti-tumor activity, especially in combination with checkpoint inhibitors and chemotherapy, into human trials in recent years.

There are currently four clinical trials being conducted at Penn, including:

- A Phase I study, led by Vonderheide, to learn if adding the investigational anti-CD40 drug RO7009789 to nab-paclitaxel and gemcitabine both before surgery and after

surgery is safe, feasible, and beneficial to patients with pancreatic cancer.

- A Phase 1b/2 study to evaluate the efficacy of the combinations of APX005M, Nivolumab, Gemcitabine, and nab-Paclitaxel or APX005M, Gemcitabine, nab-Paclitaxel in treating patients with metastatic pancreatic adenocarcinoma. The principal investigator is Mark O'Hara, MD, an assistant professor of Hematology Oncology.
- Using the immuno-activating monoclonal antibody called APX005M, administered in combination with nivolumab to adults with metastatic melanoma. The Phase 1/2 trial is led by Gerald P. Linette, MD, PhD, the chief medical officer for Cancer Immunotherapy and clinical director of the Sean Parker Institute.
- A study of the anti-CD40 drug APX005M in adults with solid tumors. The principal investigator is Dr. Ronac Mamtani, MD, MSCE, an assistant professor of Hematology Oncology.

Additionally, Abramson Cancer Center researchers are planning trials using this approach in patients with advanced and metastatic solid tumors.

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