Synthetic DNA-encoded checkpoint inhibitor antibodies advance cancer immunotherapy

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Wistar scientists and collaborators demonstrate for the first time that through engineering constructs, they can express DNA-encoded monoclonal antibodies (DMAbs) targeting CTLA-4, an important cancer checkpoint molecule that blocks anti-cancer immunity. Using a synthetic DNA platform, they built versions of the anti-CTLA-4 molecule and were able to then deliver the DMAbs and have them generate fully functional anti-CTLA4 molecules in vivo. This proof-of-principle study opens new avenues for the design and delivery of therapeutic checkpoint inhibitors and suggests potentially novel applications of this technology in cancer treatment. Study results were published online in *Cancer Research*.

Treatment of cancer with checkpoint inhibitors has recently revolutionized cancer immunotherapy. Since the discovery of immune checkpoints, which was recognized as a groundbreaking development for cancer therapy and awarded the Nobel Prize in physiology or medicine this week, checkpoint inhibitors are becoming standard of care for various malignancies, showing unprecedented impact for patients.

Despite the tremendous advancement in cancer therapy brought by monoclonal antibodies targeting checkpoint molecules, manufacturing complexity and repeated dosing may limit a broader use of this technology.

"Our work provides the first demonstration that we can use synthetic DNA technology to produce checkpoint inhibitor molecules in vivo to impact tumor growth in a preclinical setting," said lead researcher David B. Weiner, Ph.D., executive vice president and director of the Vaccine & Immunotherapy Center at The Wistar Institute, and W.W. Smith Charitable Trust Professor in Cancer Research. "We showed that DMAbs may represent a valuable addition to the cancer immunotherapy toolbox: In our preclinical studies, DMAbs achieved antitumor activity comparable to that of traditional monoclonal antibodies, while being delivered through a simpler formulation that may provide a bridge to expand target populations for checkpoint inhibitors."

The team developed a synthetic, sequence-optimized DNA plasmid designed to encode anti-mouse CTLA-4 monoclonal antibodies. When injected in the muscle of mice with the aid of an electroporation device to enhance uptake, the anti-CTLA-4 DMAbs resulted in significant and prolonged antibody expression with even a single dose. Importantly, this approach stimulated robust CD8+ T-cell infiltration, achieving tumor clearance across multiple mouse tumor models. The researchers then went on to develop human checkpoint inhibitor molecules and demonstrated their production in mice and their ability to stimulate human T-cell responses associated with antitumor activity.

"Our results open the door for further applications of DMAbs in cancer immunotherapy," said Elizabeth K. Duperret, Ph.D., postdoctoral fellow in the Weiner Lab and first author on the study. "This platform is rapid and flexible, allowing for further optimization of antibody sequences, including development of novel therapeutic approaches for which conventional monoclonal antibodies are not suitable."

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