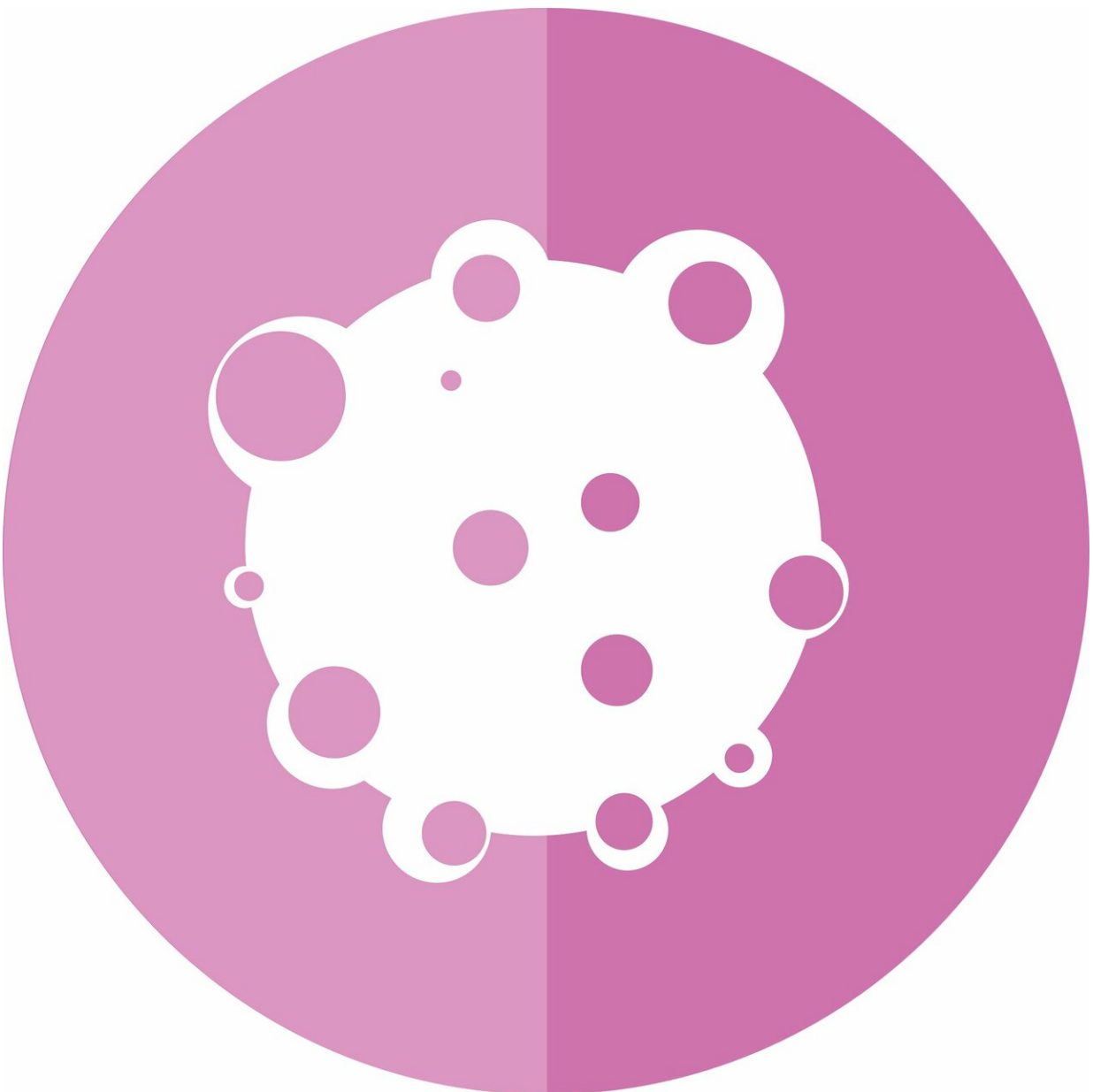


Anticancer immunity through tumor antigen identification and conversion to DNA vaccines

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Wistar scientists and collaborators demonstrated the utility of an optimized synthetic DNA vaccine platform for rapidly inducing immunity against unique combinations of tumor neoantigens. These results reveal a direct pathway to effectively tackling the tumor variability that presents enormous challenges for the development of effective immune strategies.

This study, published online in *Cancer Immunology Research*, advanced the techniques for rapidly screening neoantigens from patients and designing [vaccine](#) cassettes that allow for simple expression of dozens of antigens in a single formulation. This personalized approach resulted in a much higher CD8+ T-cell immunity than that achievable through other approaches. It also provided a simple, consistent and potent system that was effective at killing [tumor cells](#), slowing [tumor growth](#) and profoundly delaying or preventing [tumor](#) progression in preclinical models of lung and [ovarian cancer](#), according to the study.

During disease progression, [cancer cells](#) accumulate a vast number of genetic mutations. This process generates novel antigens, called neoantigens, that are not present in normal cells and can, therefore, be a target for the immune response. The major goals for an effective individualized treatment of [cancer](#) patients would be to rapidly identify the unique set of neoantigens expressed on a patient-specific basis and use this information to build a matched diverse collection of antigens into a vaccine that can be simply and repeatedly administered to that patient to generate CD8+ killer T cells.

"Neoantigens are a highly promising field of investigation," said corresponding author David B. Weiner, Ph.D., executive vice president of The Wistar Institute, director of Wistar's Vaccine & Immunotherapy Center, and W.W. Smith Charitable Trust Professor in Cancer Research. "Prior strategies were limited in several aspects, including the number of neoantigens they could encode in one vaccine and the speed with which the vaccine could be generated. Most of these prior vaccines generated a lower percentage of CD8 killer T cells, which are the 'Navy SEALs' of the immune system that can hunt and destroy the patient's specific cancer."

In this study, Weiner and colleagues utilized a rapid approach to identify new antigens and their degree of expression in the tumors and then used advanced molecular tools to "sew" dozens of the identified neoantigens into cassettes that were optimized for expression and processing in a way that would result in high presentation to the immune system.

"The speed of development of previous approaches was considerably slower," added Weiner. "We have developed a simple format for rapid development of patient-specific cancer vaccines targeting antigens derived from their tumors and provided a proof of principle for this novel approach."

The team started by sequencing tumors from three different mouse models of lung and ovarian cancers and identifying the mutations that generate unique neo-epitopes, or bits of proteins that are altered or not present in the corresponding non-mutant molecule. They then designed DNA plasmids, each encoding a string of 12 of these epitopes, for a total of seven DNA vaccines and 84 neo-epitopes.

These DNA vaccines were delivered in mice using controlled CELLECTRA electroporation in order to enhance their potency. In contrast to prior approaches, in this study 75% of the epitopes driven by

the vaccine were targeted by CD8+ T cells. This illustrates that platform limitations, synthetic DNA design and specifics of delivery can all impact the immune response outcome.

Importantly, T cells isolated from the immunized mice and co-cultured with tumor cells only attacked and killed [cells](#) from their corresponding tumor type, demonstrating the high specificity of their cytotoxic activity. Researchers tested the vaccines in tumor-bearing mice and observed a profound delay in tumor progression and a significant increase in survival after vaccination.

"Because of the dynamic nature of cancer mutations, which tend to be passenger mutations, targeting multiple neoantigens simultaneously is critical for the success of immunotherapy as it reduces the likelihood of tumor escape," said Alfredo Perales Puchalt, M.D., Ph.D., postdoctoral fellow in the Weiner Lab and co-first author on the study. "Our promising preclinical results warrant further development of this personalized medicine approach."

More information: Synthetic DNA multi-neoantigen vaccine drives predominately MHC class I CD8+ T cell mediated effector immunity impacting tumor challenge, Cancer Immunology Research (2018). Advanced online publication.

Provided by The Wistar Institute

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