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Wistar Scientists Develop Two-Vaccine Strategy to Fight T Cell Lymphoma

PHILADELPHIA — (MAR. 10, 2026) — T cell lymphomas are notoriously difficult to treat because immunotherapy, despite being one of the most effective therapies for treating cancer, can't easily distinguish cancerous T cells from healthy ones. Now, scientists at The Wistar Institute have designed a two-vaccine approach that not only targets the tumors' unique molecular identity but counters the evasion strategy the cancer employs in response. Their findings, published in *Cancer Immunology, Immunotherapy*, demonstrate that combining a vaccine targeting the cancer's T cell receptors (TCR) with a second vaccine targeting cancer-specific mutations significantly improves tumor control and survival in preclinical models. The approach offers hope for treating one of oncology's most intractable blood cancers.

T cell lymphomas (TCLs) account for roughly 10% of all non-Hodgkin's lymphomas and are associated with poor prognosis: Patients who relapse early after treatment face a five-year survival rate of just 11%. While immunotherapies have revolutionized the treatment of solid tumors and B cell cancers, they have had limited results in TCLs, in part because T cell cancers arise from the very immune cells that the majority of immunotherapies are designed to recruit. Treating a T cell cancer with T cell–based therapy requires the ability to distinguish between healthy T cells and cancerous ones—and to precisely target the latter.

The Wistar team, led by 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 Distinguished Professor in Cancer Research, and first author Pratik S. Bhojnagarwala, Ph.D., postdoctoral fellow in the Weiner Lab, identified a critical vulnerability in the biology of T cell cancers: clonality. When a T cell becomes malignant, it replicates by cloning itself, which results in every cancer cell carrying an identical T cell receptor (TCR) on its surface. That shared "fingerprint" became the researchers' first target.

"As a T cell becomes cancerous and transforms into a lymphoma, all those new cancerous cells are going to have the same T cell receptor on their surface," said Bhojnagarwala. "That provides an opportunity from a therapy design standpoint: You can design these vaccines very specifically to target just the T cell receptor of that cancerous T cell and leave the healthy T cells alone."

In collaboration with biotherapeutics company Geneos Therapeutics, the team engineered a synthetic DNA (synDNA) vaccine called TCRfullvax, encoding the three TCR chains (i.e., protein subunits comprising the receptor) expressed by a well-established murine model of T cell lymphoma, EL4. When administered via Wistar's synDNA neoantigen platform, the vaccine induced robust immune responses against all three TCR chains. Immunological analysis confirmed that the responses were specific: Vaccinated preclinical models showed no loss of healthy T cells, supporting the strategy's selectivity. Further, TCRfullvax delayed tumor growth and improved survival. However, over time, the tumor cells began to downregulate their TCR

expression, effectively hiding the antigen that the vaccine was designed to find and decreasing the effectiveness of the vaccine.

To counter that evasion technique, the scientists developed a second vaccine—EL4neovax—targeting 15 neoantigens (i.e., mutated proteins found only in the tumor cells due to DNA copying errors). Because neoantigens are absent from healthy cells, they represent additional, highly specific targets for immune attack. EL4neovax elicited strong immune responses against 5 of the 15 encoded neoantigens and independently controlled tumor growth.

When the two vaccines were administered together, the results were significantly better than either approach alone. Murine models receiving the combination therapy showed superior tumor control and improved survival compared to control groups. Bhojnagarwala explained that the therapy's effectiveness was due to lessening the tumor's ability to adapt to treatment.

"The idea behind giving both vaccines together is that you are able to kill more of the cancerous cells initially, giving the tumor less time to evolve these different evasion mechanisms and lose whatever antigens we are targeting," said Bhojnagarwala. "Having this two-pronged approach basically gives the tumor less time to escape."

The findings build on Wistar's established synDNA neoantigen platform, which has previously shown the ability to encode and deliver up to 40 distinct neoantigens simultaneously. The current study represents the platform's first application to a T cell malignancy.

"This study continues to expand the potential uses of neoantigen immunotherapy," said Weiner. "We're starting to appreciate how different everyone's cancers are and to better match treatment to the response of the particular type of patient and the type of cancer they have. This is another example of that type of next-generation tool to improve outcomes in cancer."

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