PRESS RELEASE

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Promising Personalized Approach to Liver Cancer Therapy Made Possible by DNA-based Neoantigen Research Designed at The Wistar Institute

Geneos Therapeutics, Wistar, and Collaborators Translate Personalized DNA Vaccine Technology into Clinical Outcome Based on Mistakes Tumors Make

PHILADELPHIA — (Tuesday, April 30, 2024) — Hepatocellular carcinoma (HCC), or liver cancer, is an aggressive malignancy with limited treatment options. An immunologically cold cancer — meaning the tumors can effectively hide themselves from the immune system — liver cancer can escape or not respond to first-line treatment options, resulting in a poor prognosis. The results of a new clinical trial published in *Nature Medicine* show that a novel, personalized neoantigen vaccine therapy demonstrated promising anti-tumor efficacy in patients with liver cancer who failed their original front-line treatment. The foundational biomedical research leading to this important study and important outcome originated from research in the Vaccine & Immunotherapy Center at The Wistar Institute.

The clinical trial was directed by the Philadelphia biotherapeutics company, Geneos Therapeutics — along with a scientific team of collaborators including The Wistar Institute — in the paper, "Personalized neoantigen vaccine and pembrolizumab in advanced hepatocellular carcinoma: a phase 1/2 trial."

Of the 36 participants enrolled, 34 were evaluable (i.e., able to be studied under the trial guidelines) among these, **eleven** demonstrated tumor regression by clinically defined Response Evaluation Criteria in Solid Tumors (RECIST), resulting in a tumor regression rate of 30.6% — supporting a response to their therapy. Of those eleven, **eight** had partial vaccine responses

(meaning their tumors decreased in size, with one such patient's tumor shrinking enough to be surgically removed), and **three** had complete responses — meaning their observable tumors were eliminated. An additional 9 patients exhibited stable disease under treatment. While not a direct clinical endpoint, these patients' disease appeared to stop progressing. The range for the median survival in months for patients with liver cancer who have failed first-line therapy is described as 12.9-15.1 months; however, the median overall survival at the time of the study's data cutoff was 19.9 months, with 17 of the participants still being monitored for overall survival at the time of publishing.

In context, the results support a significant increase in survivorship for patients with this notoriously aggressive & difficult-to-treat cancer compared to historical endpoints. Though Phase 1/2 safety and efficacy studies are an important initial step in clinical advancement of a new therapeutic, these notably positive results open the possibility for additional research to be conducted to evaluate the use of the team's neoantigen vaccine in expanded HCC cancer studies as well as to extend this technology to additional cancers.

The host immune system has powerful immune surveillance effectors termed "Killer T cells," or CTLs, which serve to eradicate foreign elements such as viruses growing in host cells by killing the entire cellular factory. However, the ability to recognize tumor antigens that are hiding in host cells is a much more difficult task. Accordingly, as cancers grow, they can overwhelm the host through increasingly rapid cell division, but they also incorporate mutations or "mistakes" in multiple of the cancer cells' protein sequences, in part due to their bypassing normal cell stringent regulatory processes. Those mutations occurring in tumors' proteins are termed neoantigens (NeoAg): proteins that are expressed uniquely in cancers as a by-product of cellular dysfunction.

Geneos scientists worked with scientists in The Wistar Institute Vaccine & Immunotherapy Center — led by **David B. Weiner, Ph.D.**, Wistar Executive Vice President, Vaccine & Immunotherapy director, and W.W. Smith Charitable Trust Distinguished Professor in Cancer Research — to conceptualize and optimize a unique gene assembly process to create highly consistent and effective NeoAg building blocks driving effector T cells consistently in vivo.

As a model for designing human NeoAg vaccine cassettes, the scientists first sequenced mouse tumor DNA and RNA and used defined AI-based approaches to identify the collection of "mistakes" that were most immune activating in any particular tumor. Assembly and clipping of each specific tumor mistake were assembled into a sequence of immune strings that used DNA

intervening sequences to physically "separate" each individual NeoAg in the string. Next, the string's ability to drive was evaluated to ensure that the placement of a particular neoantigen along the string was capable of retaining its immune potency. They documented that the final cassette strings as DNA vaccines induced potent induction of T cell immunity and could regress and clear tumors in preclinical model studies. Without the NeoAg vaccination, the control models' immune systems ignored tumors when challenged which grew unabated in these animals. They then studied sequences derived from human tumors as well to further advance this research towards the clinic.

While neoantigens produced by liver cancer don't typically trigger strong immune responses, the team hypothesized that their improved neoantigen vaccine strings as well as the inclusion of immune-stimulating signals that the lab had developed could train the immune system to better recognize and eradicate the malignancy.

Accomplishments in the lab validated the utility of assembling specifically designed larger collections of NeoAgs in a single vaccine (40Ags), including specific processing signals to preserve the integrity of each potential NeoAg in the string. The team's technology was also able to include specific T cell expansion signals associated with activation of CD4 and CD8 Killer T cell immunity built into the vaccines' DNA designs, among other innovations; these design elements showed that the technologies were well tolerated and could protect preclinical models from cancer challenge.

"We're very pleased to have played a role, working together with Geneos and the entire team in advancing this important, exciting technology and to see its impact in patients in the important GT30 clinical trial," said **David B. Weiner, Ph.D.** "Advancing the next generation of nucleic acid immune weapons for impacting intractable cancers is a major focus of our team."