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ABSTRACT BOOK

Non-natural MUC1 Glycopeptide Homogeneous Cancer Vaccine with Enhanced Immunogenicity and Therapeutic Activity

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Glycopeptides derived from the glycoprotein Mucin-1 (MUC1) have emerged as promising tumor-associated antigens for cancer vaccine research and development.[1] However, their low immunogenicity, combined with non-selective conjugation to carrier vehicles such as proteins or nanoparticles, presents a significant challenge to the efficacy of MUC1-based vaccines in clinical settings.[2] In this study, we introduce a novel vaccine candidate based on an artificial MUC1 glycopeptide incorporating (4*S*)-4-fluoro-L-proline and *S*-(α-D-GalNAc)-thiothreonine,[3] which is site-specifically conjugated to the immunogenic protein carrier CRM_{197} (Figure 1). This conjugation method involves selective reduction and subsequent re-bridging of one of CRM_{197} disulfide bridges, allowing for the integration of one copy of the non-natural MUC1. This strategy preserves both the structural integrity and immunogenicity of CRM_{197}. The resulting vaccine is chemically defined and homogeneous, eliciting a robust Th1-like immune response in mice. Moreover, it generates antibodies capable of recognizing human cancer cells expressing tumor-associated MUC1 on their surface. Importantly, this vaccine demonstrates significant efficacy in delaying tumor growth and improving the survival of tumor-bearing mice when administered as a standalone prophylactic or therapeutic treatment, with or without combination with a checkpoint inhibitor. The combined advantages of synthetically designed non-natural antigens and site-specific conjugation offer promising avenues for vaccine design with reduced batch-to-batch variation, increased immunogenicity, and enhanced therapeutic potential.

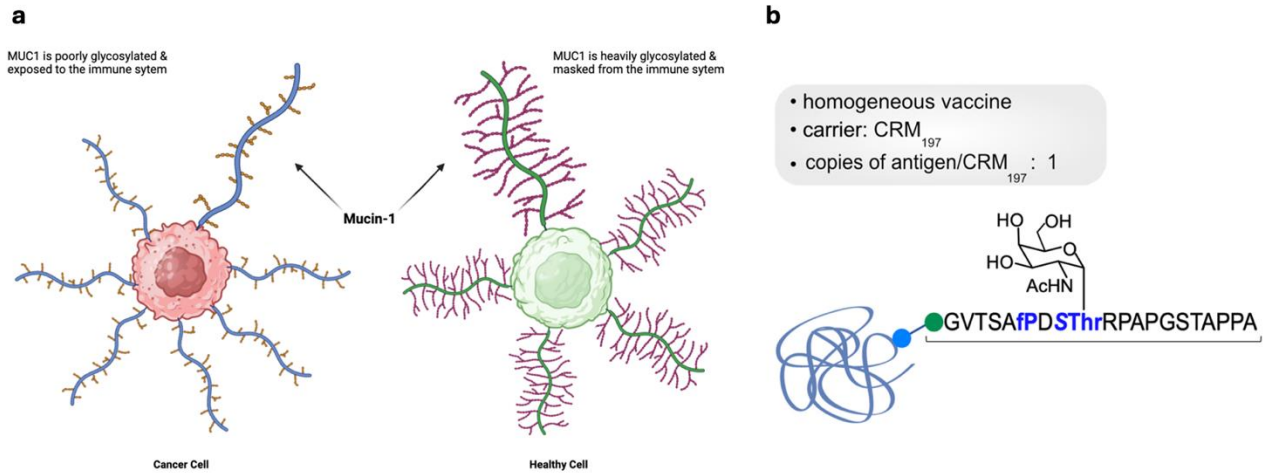

Figure 1. (a) Schematic depiction of the different post-translational modifications of the MUC1 in cancer and healthy cells. (b) Properties & futures of the current vaccine candidate.

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References:

1. Hollingsworth, M.; Swanson, B. *Nat. Rev. Cancer.* **2004**, *4*, 45.
2. Roy, R.; Mousavifar, L. *Chem. Soc. Rev.* **2023**, *52*, 3353.
3. Compañón, I.; Guerreiro, A.; et at. *J. Am. Chem. Soc.* **2019**, *141*, 4063.