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SUMMARY

DEVELOPMENT OF BISPECIFIC ANTIBODY FOR TREATMENT OF CANCER

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As a third-year student in the Medical and Pharmaceutical Biotechnology program taught in English at the University of Applied Sciences in Krems, Austria, I am required to complete a 6-month practical internship that serves as the basis for my bachelor's thesis. I chose to complete my internship in the Marasco Lab at the Dana-Farber Cancer Institute in Boston focused on the development of a new bispecific antibody for the treatment of various solid tumors. In addition to learning countless experimental techniques including FACS, molecular biology, and bioassay development, working on this project has furthered my development as a young scientist by encouraging me to think critically about my work while analyzing data and planning future experiments. I was also able to gain valuable clinical experience by assisting with the lab's influenza project, where I helped blood donors complete informed consent and study questionnaire documents and escorted them for their blood draws.

In a healthy individual there is a constant cycle of cellular regeneration as old or damaged cells are removed through programed death and replaced with new ones. The formation of a tumor occurs when cells start to divide uncontrollably and left unchecked, they will eventually metastasize and invade other tissues. The body's immune response is modulated by receptors called immune checkpoints (IC). While immune checkpoints play a critical role in immune tolerance and are responsible for protecting healthy cells from the immune system, cancer cells overexpress a wide range of IC molecules on their surface allowing them to hijack these pathways and evade immune recognition.

Checkpoint blockade inhibitors block these interactions by stopping inhibitory signals in immune cells, allowing the immune system to recognize and eliminate the tumor. Monoclonal and bispecific antibodies have been proven successful when blocking immune checkpoints to treat cancer, however many patients do not experience complete responses due to a lack of T cell infiltration and a highly immunosuppressive microenvironment. To improve the number of patients that experience complete or durable responses, combination checkpoint blockade therapies such as anti-PD(L)1/anti-TIGIT are currently being tested in clinical trials.

TIGIT was discovered in 2009 and it belongs to the family of PVR like proteins. It has one extracellular immunoglobulin variable domain, a type I transmembrane domain, and a short intracellular domain with one immunoreceptor tyrosine-based inhibitory motif (ITIM) and one immunoglobulin tyrosine tail (ITT)-like motif (1). It is expressed on activated $CD8^+$ T and $CD4^+$ T cells, NK cells, regulatory T cells (Tregs), and T helper cells, allowing it to regulate both innate and adaptive immunity (2). TIGIT's cognate ligands are CD155 and CD112, which are naturally expressed on antigen presenting cells, with the role of downregulating T cell and natural killer cell function. Previous studies have shown that TIGIT blockade could overcome solid and hematological cancers and based off these results, clinical trials investigating TIGIT blockade are currently ongoing. Though some studies are testing TIGIT as a monotherapy, the vast majority of current studies are testing it in combination with anti-PD-1/PD-L1 mAbs for the treatment of patients with advanced solid malignancies (1).

Bispecific antibodies are designed to target multiple pathways at once by combining the binding domains from two antibodies onto a single framework, enabling them to simultaneously engage multiple targets. Even though clinical trials for dual PD-L1/TIGIT blockade are still ongoing and they showed superior clinical benefits that PD-L1 blockade alone, their efficiency is still being tested. The data presented suggest that PD-1/TIGIT could be used when PD-1 as a monotherapy fails to improve the outcome of treatment.

This study aimed to develop a BsAb that simultaneously binds to TIGIT and PD-1, therefore blocking interaction with CD155 and PD-L1 respectively. The study shows promising results comparing the difference between bispecific and monoclonal antibodies. To design the bispecific antibody, monoclonal antibodies were first tested and contact residues were identified via alanine scanning of the CDRs. After choosing few of the residues, bispecific antibodies were designed and tested for CD155 blockade and compared to monospecific antibodies. Bispecific antibodies showed significant improvement in blockade, reaching levels comparable to that of a commercial control currently in clinical trials.

References:

1. Harjunpää H, Guillerey C. TIGIT as an emerging immune checkpoint. Vol. 200, Clinical and Experimental Immunology. Blackwell Publishing Ltd; 2020. p. 108–19.
2. Chauvin JM, Zarour HM. TIGIT in cancer immunotherapy. Vol. 8, Journal for ImmunoTherapy of Cancer. BMJ Publishing Group; 2020.