Development of Immune Checkpoint Inhibitors in Cancer Therapy Based on Nanobody Technology

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Cancer is a leading cause of death, posing a significant socioeconomic burden worldwide. Immune checkpoint inhibitors targeting PD-1/PD-L1 or CTLA-4 using monoclonal antibodies have brought about major advances in cancer therapy. However, there are existing limitations of monoclonal antibody technology, including poor tumor penetration, significant adverse effects, reduced efficacy over time, and high treatment costs. Nanobodies, also known as VHHs, with their extremely small size, high stability, low toxicity, ease of production, and flexibility for multivalent engineering, have emerged as a promising alternative for conventional antibody technology in cancer therapy research. The study aims to develop a bispecific nanobody capable of simultaneously targeting human PD-L1 (hPD-L1) and human CTLA-4 (hCTLA-4). To achieve this objective, firstly, a panel of published nanobodies capable of inhibiting hPD-L1 and hCTLA-4 was constructed. Next, ELISA assays were conducted, in which 2 nanobodies with high affinity were selected to develop the bispecific nanobody capable of binding to 2 checkpoints. Finally, the binding affinity of the bispecific nanobody to both targets was evaluated. The results demonstrated that a panel of 5 anti-hPD-L1 and anti- hCTLA-4 nanobodies was successfully expressed and purified. ELISA screening showed that VHH9 exhibited the highest affinity to hPD-L1 (EC50= 3.74 nM), while VHH02F4 showed the highest affinity to hCTLA-4 (EC50= 2.52 nM). The bispecific nanobody VHH02F4-9 showed improved affinity to the 2 checkpoints compared to monovalent forms (EC50 = 2.63 nM, to hPDL-1; EC50 = 0.34 nM to hCTLA-4). Current research orientation is evaluating the functional inhibitory activity of the novel bispecific nanobody against hPDL-1 and hCTLA-4.

Awards Won: