Computational Modeling of Bispecific Antibodies Targeting CD30+ Cells in Hodgkin Lymphoma and Anaplastic Large Cell Lymphoma

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Every year, approximately 90,000 people in the United States are diagnosed with lymphoma, a cancer impacting white blood cells called lymphocytes. The CD30 receptor, overexpressed in Hodgkin Lymphoma and Anaplastic Large Cell Lymphoma, is essential for cell proliferation and survival, making it a critical therapeutic target. The CD3 epsilon receptor subunit is found on immunocompetent lymphocytes and stimulates the immune response when exposed to specific antigens. Immunotherapeutic advancements have proven that bispecific antibodies (bsAbs) can bind to two antigens simultaneously, facilitating immune cell-mediated cytotoxicity. Despite advances, bispecific antibody research remains largely experimental, with an insufficient use of computational and AI tools in development. This study hypothesized that computational analysis of Fab regions could help recognize those that bind to the CD3 epsilon and CD30 receptors of CD8+ cells and lymphoma cells, respectively, promoting cancer cell death. Molecular docking simulations provided the Fab binding structures with CD3 epsilon and CD30. Docking was validated using ScanNet, a deep-learning tool. Visual inspection, hydrogen bond count, and binding energy were used as selection criteria. Out of a fixed set of Fab regions (n=10), Fab 1IQW displayed the highest binding affinity (-25.6 kcal/mol) and the most hydrogen bonds (28) with the CD3 epsilon receptor. For the CD30 receptor, 1A5F exhibited the strongest binding affinity (-23.0 kcal/mol) but formed fewer hydrogen bonds (7). This research will pave the way for engineering bsAbs targeting various receptors, including CD30 and CD3 epsilon, while demonstrating the potential of computational techniques for bsAb development.

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