Bioengineering an Antibody Drug Conjugate for Uveal Melanoma

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Uveal melanoma, cancer of the melanin-producing cells in the eye, is the most common type of intraocular cancer in adults. Approximately half the patients develop metastatic disease, which has only two FDA approved therapies. The high mortality rates indicate a need for a therapy that can better treat metastatic uveal melanoma. Antibody Drug Conjugates (ADCs) are one of the fastest growing anti-cancer therapies, consisting of three main components: a monoclonal antibody, linker, and cytotoxic drug. ADCs bind to specific antigens, travel inside the cell, and deliver a cytotoxic drug—resulting in fewer side effects. GD2, an antigen found on melanoma cells, is a prime target for treatment. A new technology explored in this research enzymatically attaches the drug to the C-terminus of the long chain of the ADC, minimizing changes to the antibody's active site. The specificity of microbial transglutaminase (mTg) ensures uniform reaction products, thereby minimizing product heterogeneity. The scope of this research is summarized in five phases: plasmid purification, protein production, transglutaminase reaction, protein binding, and in vitro testing. The data collected thus far from these phases demonstrates high recoveries for both plasmids, the largest being for the light chain plasmid at 1237 ng/µl—quality assured by restriction digest. UV scans and SDS-PAGE gels indicate antibody recovery for positive control antibody but no recovery for anti-GD2 antibody. Currently, overlap extension PCR is being used to produce a bicistronic construct for anti-GD2 antibody production. These bioengineered dye-coupled antibodies offer a model for developing ADC-based therapies for uveal melanoma.

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