Next-Generation Cancer Therapeutics: Enhancing Anti-Tumor Specificity of Antibody Drug Conjugates by N297Q Deglycosylation

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Despite tremendous progress in oncology, many treatments such as chemotherapy continue to weaken the immune systems of cancer patients, increasing their susceptibility to infections and other diseases. This has heralded a novel class of cancer therapeutics called antibody drug conjugates (ADCs) that couples the targeting ability of monoclonal antibodies with a highly potent cytotoxin designed to trigger apoptosis upon internalization by cancer cells. But despite this targeting specificity, it is not uncommon for healthy leukocyte receptors (FcγRs) to bind to the Fc region of the ADC antibody. This increases the destruction of healthy leukocytes and prevention of ADC internalization—potentially crippling side effects for cancer patients whose immune systems are already compromised by treatment drugs. We hypothesized that ADC deglycosylation via a N297Q point mutation would induce a structural alteration of the Fc region that will inhibit FcγR binding. To test this, we used a Biacore biosensor to develop immunoassays for measuring the binding affinities of wild-type and deglycosylated ADCs to universal receptors FcγRI, FcγRIIa, and FcγRIIb. Varying surface plasmon resonance (SPR) signals established differences in refractive index directly proportional to the concentration of Fcγ receptors bound to each and were converted into resonance units (RUs). Analysis of protein-protein interaction models revealed that FcγR binding to ADCs was decreased by up to 98%, supporting the utility of deglycosylation in enhancing targeting specificity and thus safety. This finding points to the promise of deglycosylated ADCs as a highly selective therapeutic that may significantly accelerate the recovery of cancer patients.