

GT-001 - ANTI-LEWIS Y ANTIBODY WITH SUPERIOR FINE-SPECIFICITY AND REDUCED OFF-TARGET BINDING

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Background The Lewis Y (CD174) carbohydrate antigen is widely expressed in primary and metastatic epithelial tumors like colon, lung, ovarian, and breast. Targeting Lewis Y for cancer therapy was pursued before, however, other anti-Lewis Y antibodies tested in clinical trials showed cross-reactivity to related carbohydrate structures expressed on blood cells and mostly failed for efficacy and/or safety reasons.¹⁻⁴ We have developed a humanized antibody (GT-001) that shows superior fine-specificity and higher affinity compared to clinically tested anti-Lewis Y antibodies BR96 and h3S193.

Methods The specificity and cross-reactivity of GT-001, BR96 and h3S193 were compared. Cross-reactivity binding to related carbohydrate PAA-conjugates was tested via ELISA and affinity towards Lewis Y-PAA was measured using switch-SENSE[®] technology (DRX2, Dynamic Biosensors). Functional binding to several tumor cell lines and healthy human leukocytes was analyzed via flow cytometry. Binding of GT-001 to different cancer indications was analyzed by immunohistochemistry. Inhibition of tumor cell proliferation was tested using GT-001 coupled to ProtG-MMAE.

Results GT-001 is strictly specific for Lewis Y and does not cross-react with >90 related carbohydrate structures tested. Our lead candidate shows superior fine-specificity compared to BR96, for which we could confirm the reported cross-reactivity towards Lewis X,⁵ and stronger binding of Lewis Y compared to h3S193 as shown by affinity measurement. Further, GT-001 shows no/weak binding to blood cells whereas BR96 and h3S193 significantly bind to different leukocyte subsets. IHC studies reveal that GT-001 stains tumor tissue of different cancer indications (breast cancer, colorectal cancer, head and neck cancer, (non) small cell lung cancer and ovarian cancer) at a high percentage of cases. In ADC surrogate assays, GT-001 potently inhibits the proliferation of several tumor cell lines indicating effective internalization.

Conclusions Lewis Y is expressed on many epithelial tumor indications of high medical need. However, several approaches of targeting Lewis Y have failed in the past for efficacy and/or safety reasons. We have developed a humanized antibody that shows superior fine-specificity and higher affinity compared to clinically tested anti-Lewis Y antibodies BR96 and h3S193. Due to the superior fine-specificity, GT-001 shows no/reduced binding of healthy leukocytes potentially reducing side effects as observed for BR96 in the clinic. Its strong target binding and internalization properties make GT-001 an ideal candidate for ADC development.

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