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ANTIBODIES SPECIFICALLY RECOGNIZING CANCER-ASSOCIATED GLYCOFORMS OF MUCIN-LIKE PROTEINS

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Background One of the most drastic changes in cancer is the altered glycosylation of proteins and lipids, giving rise to truncated or highly fucosylated and highly sialylated glycans which are almost absent on normal cells. Thus, developing antibodies against protein/carbohydrate combined epitopes (GlycoTargets) comprising these tumor-specific glycans enables highly potent therapies with reduced off-tumor toxicity and allows targeting of otherwise 'undruggable' normal-tissue expressed proteins.

Multiple EGF-like-domains 9 (MEGF9) is a transmembrane protein mainly expressed by immune cells and cells of the nervous system and has been associated with carcinogenic features in breast cancer and soft tissue tumors. Podocalyxin (PODXL) is a cell surface sialomucin normally expressed in several tissues including kidney and vascular endothelium, but it is also overexpressed in many cancers especially of epithelial origin. Both of these proteins contain mucin-like domains with a high density of potential GlycoTarget epitopes. Using our proprietary platform technology, we have developed antibodies against these two glycoproteins, which only bind to the respective tumor-associated glycoform of their target, thereby reducing recognition of the protein expressed on healthy cells.

Methods Recombinantly expressed target glycoforms were characterized by mass spectrometry and used to analyze the specificity of our antibodies for the respective O-glycosylated target in an ELISA format. Antibody specificity was further confirmed using our proprietary cell lines with distinct glycosylation patterns as well as tumor cell lines and human immune cells expressing varying levels of MEGF9 or PODXL. Furthermore, binding to healthy and tumor tissues was analyzed by immunohistochemistry.

Results We have successfully generated two different antibodies, which recognize PODXL and MEGF9, respectively, only if a specific tumor-associated glycan is present. Both clones do not cross-react with their non-glycosylated target or the carbohydrate structure on other carrier-proteins as confirmed by ELISA and flow cytometry. Our antibodies recognize various tumor cell lines as well as tumor tissues in a target-specific manner, but show drastically reduced binding to healthy cells compared to conventional protein-binding control antibodies.

Conclusions Our platform technology is suitable to target protein/carbohydrate combined epitopes with specific antibodies. We successfully generated two antibodies which target distinct, tumor-specific epitopes on two mucin-like proteins, respectively, comprising a tumor-associated glycan in combination with the specific target protein. Due to this glycan dependency, our antibodies show markedly decreased off-tumor binding which may improve safety for highly potent therapeutic approaches like ADCs, CARs or radiopharmaceuticals.

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