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TARGETING OF A CANCER-ASSOCIATED LYPD3 GLYCOFORM FOR TUMOR THERAPY

Patrik Kehler*, Theresa Neumann, Anika Jaekel, Johanna Gellert, Antje Danielczyk, Lisa Weiß, Luisa Willmann, Stephanie Gurka, Naomi Kast, Manon Weiske. *Glycotope GmbH, Berlin, Germany*

Background LYPD3 (C4.4A) is a glycosylphosphatidylinositol (GPI)-anchored, highly glycosylated cell surface protein that was first described as a metastasis-associated protein.¹ Since then, it has been associated with carcinogenesis in several different cancers and is reported to be overexpressed in squamous cell carcinoma (SCC) of the head and neck, esophageal SCC, colorectal cancer as well as non-small cell lung cancer. However, it is also highly expressed in healthy epithelia of the proximal digestive tract, female reproductive organs as well as skin keratinocytes.² This may cause unwanted side effects in cancer therapy with an antibody unable to discriminate between cancer-associated LYPD3 and LYPD3 in normal tissue.

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.³ Therefore, targeting protein/carbohydrate combined epitopes (GlycoTargets) comprising these specific glycans offers reduced off tumor toxicity, which is key for highly potent therapies. We have developed an antibody which binds to tumor-associated LYPD3 in an O-glycosylation-dependent manner and shows superior tumor specificity compared to conventional protein-binding anti-LYPD3 antibodies.

Methods The specificity of our antibody for glycosylated LYPD3 was determined using differentially glycosylated proteins in an ELISA format and confirmed using cell lines with specific glycosylation patterns as well as tumor cell lines expressing varying levels of LYPD3. Furthermore, binding to healthy and tumor tissues was analyzed by immunohistochemistry.

Results We have generated an anti-LYPD3 antibody that binds to its target protein only if a specific tumor-associated carbohydrate is present. It does not cross-react with non-glycosylated LYPD3 or the carbohydrate structure on other carrier-proteins. The carbohydrate-dependent anti-LYPD3 antibody called GT-002 binds to various tumor cell lines and stains tumor tissues of different cancer indications. Notably, GT-002 elicits markedly reduced binding to normal human tissues compared to anti-LYPD3 polyclonal control antibodies or Lupatumab, an anti-LYPD3 antibody previously in clinical development as ADC (BAY1129980).

Conclusions By using our expertise in cancer-associated glycosylation, we successfully generated GT-002, a highly tumor-specific anti-LYPD3 antibody that targets neither glycan nor LYPD3 protein alone, but only the combination thereof – a tumor-specific protein/carbohydrate combined epitope on LYPD3. By using this approach, we were able to develop an anti-LYPD3 antibody that stains cancer tissue of various indications while showing drastically reduced off-tumor binding towards healthy LYPD3-positive tissues. We believe that this highly specific antibody is exceptionally suitable for potent therapies like ADCs, radio-conjugates and CARs.

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