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A humanized Claudin-1 specific monoclonal antibody for treatment of hepatocellular carcinoma

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Background: Hepatocellular carcinoma (HCC) is the fastest rising and third leading cause of cancer death. While new therapeutic modalities have been recently approved, treatment response and survival in patients remain poor. Claudin-1 (CLDN1) is a cell membrane protein mediating cell-cell adhesion, fate and differentiation. Functionality of CLDN1 in solid tumors including HCC has been demonstrated by gain- and loss-of-function studies, yet its impact as a therapeutic target is unexplored.

Aims and Method: Using humanized monoclonal antibodies (mAbs) targeting specifically the extracellular loop of human non-junctional CLDN1 and a large series of patient-derived cell-based and animal model systems we aimed to investigate the role of CLDN1 as therapeutic target for treatment of HCC.

Results: Here we show that humanized monoclonal anti-CLDN1 mAbs robustly and significantly inhibit growth, migration and invasion of tumor cells in cell line-based models of HCC and patient-derived HCC spheroids. Moreover, the robust effect on tumor growth was confirmed *in vivo* in a large series of cell line derived xenograft (CDX) and patient-derived xenograft (PDX) mouse models. Functional studies in patient-derived and cell line-based tumor spheroids revealed that the mAbs perturbed the 3D tumor architecture. Furthermore, CLDN1 mAbs markedly and significantly suppressed epithelial-mesenchymal transition (EMT) and matrix metalloproteinase synthesis in tumor cells. Good treatment response in PDX models correlated with expression of genes that are associated with a fibrotic tumor environment, whereas presence of the angiogenic factor VEGFB predicted low treatment efficacy. Treatment with humanized anti-CLDN1 mAbs is considered to be safe, as administration in non-human primates and mouse models did not reveal any major toxicity even when high doses largely exceeding the therapeutic need were repeatedly applied.

Conclusion: These results provide robust pre-clinical proof-of-concept for humanized CLDN1-specific mAbs for treatment of HCC and pave the way for clinical development of CLDN1-targeting therapies using monoclonal antibodies. The unique

and different mechanism of action provides opportunities to break the plateau of limited response and survival offered by currently approved therapies.

Figure: N/A