Background Claudin (CLDN) 18.2 is a transmembrane tight junction protein that is expressed in stomach epithelia. CLDN18.2 expression is significantly elevated in gastric and pancreatic adenocarcinomas. Loss of cell polarity in tumors results in CLDN18.2 localization to surfaces that are more readily accessible to biologics and effector cells. This expression pattern makes it an excellent target for immune stimulating antibody conjugate (ISACs), which combine the specificity of a tumor-targeting antibody with potent immune stimulation. The delivery of ISACs to the tumor microenvironment triggers the innate and adaptive immune system to attack CLDN18.2-expressing tumors. T cell priming following phagocytosis of CLDN18.2-expressing tumor cells in the context of immune stimulation results in epitope spreading and the targeting of CLDN18.2-negative tumors cells with durable immunologic memory. These mechanisms differ from other cytotoxic payloads, which rely on the induction of apoptosis or cell death to kill tumor cells. Herein, we describe the development of a Claudin 18.2 ISAC with a TLR7/8 linker-payload.

Methods For human in vitro assessment of ISACs, PBMCs or myeloid APCs were isolated from human healthy donor blood and activation was measured by flow cytometry, cytokine-bead array, and other ELISA-based methods. In vivo assessment of antitumor activity was performed using the PATU-8889s (endogenously expressing CLDN18.2) and MC38-muCLDN18.2 (engineered to express mouse CLDN18.2). Tolerability of a mouse CLDN18.2 binding ISAC was performed in healthy C57BL/6 mice.

Results CLDN18.2 ISACs elicit robust tumor antigen-dependent activation of the immune system as measured by the secretion of proinflammatory cytokines TNFa and IL-12p70. Furthermore, a CLDN18.2 ISAC significantly inhibited tumor growth in a syngeneic model with CLDN18.2 expression levels consistent with those measured in the clinical setting. Interestingly, tumor regression was also observed in a model where only approximately 15% of tumor cells expressed CLDN18.2. Furthermore, the CLDN18.2 ISAC elicited T cell-dependent immunological memory with epitope spreading, as evidenced by a lack of tumor growth upon rechallenge with the original tumor cell line lacking CLDN18.2 expression. An exploratory mouse toxicity study revealed that the CLDN18.2 ISAC was well tolerated following two doses at 60 mg/kg, and the MTD was not reached in this study.

Conclusions We believe that this is the first reported CLDN18.2 ISAC that demonstrates potent anti-tumor activity, induction of immunological memory with epitope spreading, and an acceptable safety profile in preclinical studies. A CLDN18.2 ISAC may offer benefits beyond other ADCs in development.

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