AI-ML-DRIVEN DISCOVERY OF COLLAGEN TRIPLE HELIX REPEAT-CONTAINING 1, CTHRC1, A NOVEL PROTEOGLYCAN FOR DISRUPTION OF STROMAL BARRIERS AND ENHANCEMENT OF IMMUNOTHERAPY RESPONSES IN DESMOPLASTIC TUMORS

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Background While checkpoint inhibitors (CPIs) such as anti-CTLA-4 and anti-PD-1/L1 have demonstrated efficacy in many solid tumor indications, those with high stromal presence have been difficult to treat. We aimed to use a proprietary machine learning/artificial intelligence platform to identify novel stromal targets that, upon targeting, will relieve this immunosuppressive barrier and increase CPI responsiveness in difficult-to-treat indications.

Methods Based on bioinformatic analysis using a large single-cell RNA atlas, we assessed cancer-associated fibroblasts (CAFs)/fibroblastic cells in cancer tissue for the identification of novel targets, including proteoglycans. Antibodies were generated by immunization of humanized mice. Lead antibodies demonstrated potent in vitro activity in inhibiting cell adhesion and reducing survival of pancreatic cancer cells in CAF conditioned media. We assessed efficacy and PD (flow cytometry and IHC) in the EMT6 orthotopic tumor model in immunocompetent mice.

Results Analysis of a large single-cell RNA atlas spanning many solid tumors identified CTHRC1 as one of the most upregulated CAF targets in the genome. CTHRC1 was also highly associated with CAFs from immune-excluded and desert-like tumor samples. Finally, we also find that CTHRC1 is highly expressed by both cancer cells and CAFs within the tumor, in key indications such as breast, ovarian, and pancreatic, with the potential for Fc-mediated depletion of both tumor and fibroblast cells. Profiling by scRNAseq of syngeneic tumor cells identified EMT6 breast cancer model as representative of human tumor, mirroring both CAF and tumor CTHRC1 expression. Assessment of efficacy demonstrated monotherapy activity with strong combination activity and enhanced survival when we combined anti-CTHRC1 mAbs with anti-PD-1.

Conclusions We have identified CTHRC1 as a novel proteoglycan expressed by both CAFs and tumor cells that appears to be an ideal target for inhibiting of stromal barrier function with therapeutic monoclonal antibodies that may also serve as ideal for targeting payloads to the tumor microenvironment. These data demonstrate the power of large scRNA atlases for novel target ID and show the potential of breaking down stromal barriers in opening up tumor microenvironments to immune attack.

Ethics Approval Animal studies were conducted in accordance with an Animal Use Protocol 6323.3 approved by the University Health Network Animal Care Committee.