CD70 (CD27 ligand) is highly expressed in multiple hematologic malignancies, such as non-Hodgkin lymphoma, multiple myeloma, and chronic lymphocytic leukemia, and is uniquely highly expressed in the solid tumor type clear cell renal cell carcinoma (ccRCC). Malignancies showing high CD70 expression have been the subject of multiple clinical trials evaluating anti-CD70 agents, such as antibodies with enhanced antibody-dependent cellular cytotoxicity and antibody drug conjugates (ADCs). The focus on high-expression indications seems to be a requirement, particularly for ADCs. We have shown previously that CTX130, a CRISPR/Cas gene-edited allogeneic anti-CD70 CAR-T is potently cytotoxic against even the lowest expressing RCC cell lines (e.g., ACHN). With this in mind, we evaluated CD70 expression in other solid tumor indications, including pancreatic, lung, and ovarian cancers, and assessed the cytostatic activity of CTX130 against cell lines derived from these tumor types. These studies show that high expression is not a requirement for potent activity for CAR-T cells as it appears to be for CD70-targeted ADCs. Further, these data highlight a translational medicine route for CTX130 in many solid tumor indications.

Figure 1: CTX130 is CRISPR Therapeutics’ First Oncology Product Candidate Targeting Solid Tumors

Abstract

Targeting Multiple Solid Tumor Types with Anti-CD70 Allogeneic CAR-T Cells

Figure 2: Publicly Available Data Shows that Multiple Tumor Types Express CD70

Public domain information outlining expression of CD70 in solid tumors. Both mRNA (TCGA, mRN) and protein analyses (Br J Cancer: 2013 Aug 20; 109(8): 676-684) show highest CD70 expression in ccRCC (blue arrows), but also expression in multiple other cancer types. Pink arrows indicate the observations in lung, pancreatic and ovarian cancers – the subjects of other data in this poster.

Figure 3: CD70 Protein Expression in Solid Cancer Cell Lines Mimics Clinical Expression

CD70 expression by FACS in cancer cell lines. As seen in clinical samples, the highest CD70 expression is seen in a ccRCC (ACHN cell) followed by pancreatic (H1975), ovarian (SKOV-3) and lung cancer (H1975). ACHN is a low expression RCC line previously shown to be effectively eliminated by our allogeneic anti-CD70 CAR-T cells (AACR, 2018). K562 is shown as a negative control for background staining. RNA-1 cells have low CD70 expression.

Figure 4: CTX130 Potency Initially Correlates with CD70 Expression, but Over Time CTX130 Shows High Potency Against Even Low-Expressing Lines

CTX130 is potent against all cell lines expressing CD70. Cell kill in the first 24 hours of exposure correlates with expression level of CD70 antigens. However, after 96 hours, cell kill is comparable across all cell lines and approaching 100%, a phenomenon not seen with other CD70-targeted agents, such as ADCs. These data provided the impetus to test the potency of CTX130 against these cell lines in vivo.

Figure 5: CTX130 Allogeneic Anti-CD70 CAR-T Cells are Highly Potent Against an H1975 Pancreas Tumor Xenograft Model

Public domain information outlining expression of CD70 in solid tumors. Both mRNA (TCGA, mRNA) and protein analyses (Br J Cancer: 2013 Aug 20; 109(8): 676-684) show highest CD70 expression in ccRCC (blue arrows), but also expression in multiple other cancer types. Pink arrows indicate the observations in lung, pancreatic and ovarian cancers – the subjects of other data in this poster.

Figure 6: CTX130 Allogeneic Anti-CD70 CAR-T Cells are Highly Potent Against an H1975 Pancreas Tumor Xenograft Model

Public domain information outlining expression of CD70 in solid tumors. Both mRNA (TCGA, mRNA) and protein analyses (Br J Cancer: 2013 Aug 20; 109(8): 676-684) show highest CD70 expression in ccRCC (blue arrows), but also expression in multiple other cancer types. Pink arrows indicate the observations in lung, pancreatic and ovarian cancers – the subjects of other data in this poster.

Figure 7: CTX130 Allogeneic Anti-CD70 CAR-T Cells are Highly Potent Against a SK-OV-3 Ovarian Tumor Xenograft Model

Public domain information outlining expression of CD70 in solid tumors. Both mRNA (TCGA, mRNA) and protein analyses (Br J Cancer: 2013 Aug 20; 109(8): 676-684) show highest CD70 expression in ccRCC (blue arrows), but also expression in multiple other cancer types. Pink arrows indicate the observations in lung, pancreatic and ovarian cancers – the subjects of other data in this poster.

Conclusions

- CD70 expression has been described in solid tumor types beyond ccRCC, but with lower expression and lower prevalence
- This lower overall expression may explain why there have been few successful attempts to use CD70-targeted agents in these other cancers
- CTX130, an CRISPR/Cas gene-edited allogeneic anti-CD70 CAR-T cell product candidate, shows high potency against CD70-expressing cell lines in vitro and in vivo, even against the lines with the lowest expression levels
- The potency of CTX130 observed across tumor xenograft mouse models suggests that CTX130 has potential against a range of solid tumor types beyond ccRCC, including lung, ovarian, pancreatic, esophageal and gastric cancers