Poster #3184

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

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Abstract

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 cell-mediated 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/Cas9 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 cytotoxic 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

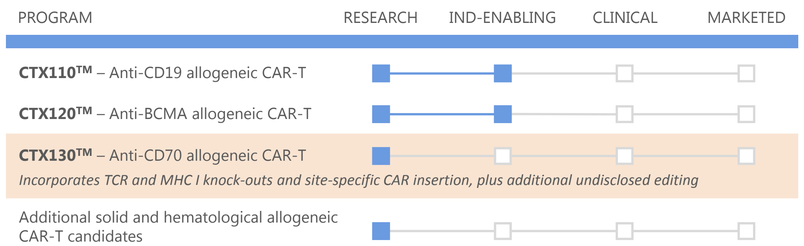


Figure 2: Publicly Available Data Shows that Multiple Tumor Types Express CD70

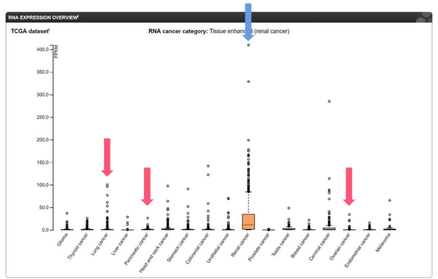


Table 2

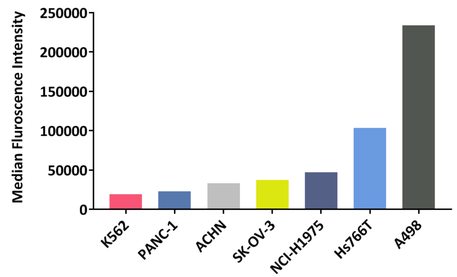
Summary of CD70 expression from tissue microarray analysis of carcinomas using 1C1

Tumor type	CD70+ of total	%CD70+
Kidney[a]	204 of 283	72
Pancreas	35 of 140	25
Larynx or pharynx[b]	18 of 82	22
Melanoma	15 of 96	16
Ovary	37 of 241	15
Lung adenocarcinoma	17 of 172	10
Colon	17 of 194	9
Breast	5 of 204	2
Brain	6 of 59	10

[a]189 of 230 (82%) clear cell carcinoma and 4 of 8 (50%) papillary carcinoma.
[b]Includes nasopharyngeal cancer.

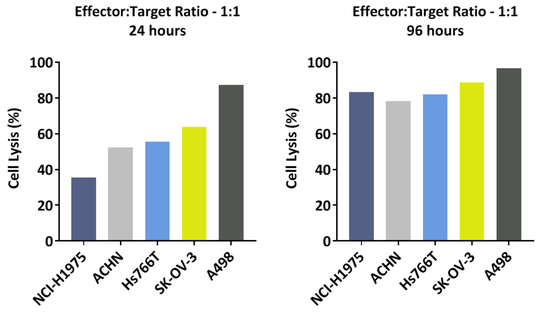
Public domain information outlining expression of CD70 in solid tumors. Both mRNA (TCGA, left) and protein analyses (Br J Cancer. 2010 Aug 24; 103(5): 676-668, right) show highest CD70 expression in ccRCC (blue arrows), but also expression in multiple other cancer types. Pink arrows indicate the observations 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



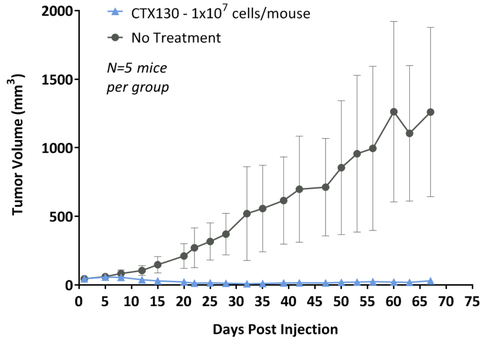
CD70 expression by FACS in cancer cell lines. As seen in clinical samples, the highest CD70 expression is seen in ccRCC (A498 cells) followed by pancreatic (Hs766T), ovarian (SK-OV-3) and lung cancer (H1975). ACHN is a low expression RCC line previously shown to be effectively eliminated by our allogeneic anti-CD70 CAR-T cells (AACR, 2018). K562 is shown as a negative control for background staining. PANC-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



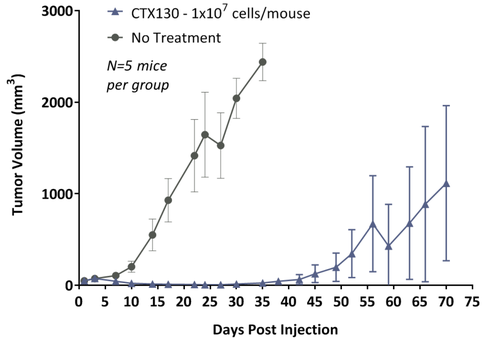
CTX130 is potent against all cell lines expressing CD70. Cell kill in the first 24 hours of exposure correlates with expression level of CD70 antigen. However, after 96 hours, cell kill is comparable across all cell lines and approaching 100%, a phenomenon not seen with other CD70-targeted agents, such 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 Hs766T Pancreas Tumor Xenograft Model



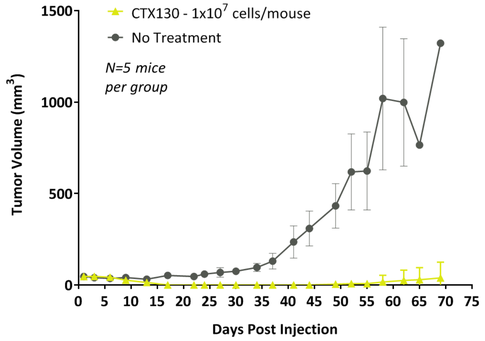
CTX130 shows potent activity against established Hs766T pancreatic cancer xenografts in mice. Durable responses are observed out past 60 days. The tumors appear to be static at this point with no sign of further growth.

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



CTX130 shows potent activity against established H1975 lung cancer xenografts in mice. Durable responses are observed out to 40 days before the tumors begin to exhibit significant growth again.

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



CTX130 shows potent activity against established SK-OV-3 ovarian cancer xenografts. SK-OV-3 has proven to be a difficult model to treat with agents targeting CD70, such as ADCs (Br J Cancer. 2010 Aug 24; 103(5): 676-684). This difficultly may come from a combination of lower antigen expression versus ccRCC cells and some intrinsic resistance to toxins used in ADCs. On the other hand, CTX130 shows high potency against SK-OV-3 cells *in vitro* and *in vivo*. In this xenograft tumor model, 4 of the 5 mice treated with CTX130 remain tumor free at the end of study.

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 so few attempts to use CD70-targeted agents in these other cancers
- CTX130, an CRISPR/Cas9 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