CTX112 and CTX131: Next-generation CRISPR/Cas9-engineered allogeneic (allo) CAR T cells incorporating novel edits that increase potency and efficacy in the treatment of lymphoid and solid tumors

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- Employee of: CRISPR Therapeutics
- Stockholder in: CRISPR Therapeutics
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Our Allogeneic CAR T Cells Share the Same Core Chassis

Allogeneic CAR T chassis:

- **Improve persistence in the allo setting** via B2M knock-out to eliminate MHC I expression
- **Avoid need** for more toxic lymphodepletion regimens
- **Reduce risk of GvHD** via TCR disruption
- **Improve consistency and safety** by precise insertion of CAR construct into TRAC locus without using lentivirus or retrovirus
CTX110 and CTX130 Allogeneic CAR T Cells Produced Deep Reductions in Tumor Burden

**CTX110 (DL2+ with re-dosing) in Non-Hodgkin Lymphoma**

- Durable CRs observed past 24 months (N=3)

**CTX130 in Cutaneous T-Cell Lymphoma**

- Change from Baseline, %

(1) Value extends beyond top of axis (215%); (2) Value extends beyond top of axis (111%)
Mean of CTX130 pharmacokinetics (n=5 DL4 subjects, first infusions only)

Durable remissions do not require long lived CAR T cell persistence, i.e., >28 days

- CAR T cells produce rapid responses: tumor regression in the first week after infusion and radiographic CRs at D28
- Allogeneic CAR T cells do not routinely persist beyond 28 days
Immune evasion edits beyond B2M KO may not improve antitumor activity

Patient NK Cells Unlikely to Limit Allogeneic CAR T Function at the Tumor Site

Tumor samples stained for NK and T cells show absence of NK cells at the tumor site

NK cells (CD56)  T cells (CD3E)

Non-Hodgkin lymphoma

Renal cell carcinoma

CAR T expansion and activity following target cell engagement far outpaces NK killing capacity in vitro

Source: Protein Atlas
Efficacy and PK data from CTX110 and CTX130 indicate that durable remissions do not require long-lived CAR T cell persistence

NK cells not observed in significant numbers at tumor sites, suggesting that increased immune evasion will have limited impact on antitumor activity

In contrast, internal and external data (e.g., Mai, et al. 2023) suggest that edits to enhance T cell function have the potential to improve efficacy

As a result, our next-generation strategy focuses on improving CAR T potency

Through systematic CRISPR screening, we identified two synergistic potency edits that we have incorporated into our next-generation CTX112 and CTX131 programs
In vivo murine T cell screen identified gene edit combinations that boost potency against solid tumors¹

Example of select combos in H1975 lung cancer xenograft model

(1) Wrocklage et. al. K3Q Therapeutics, Presented at Society for Immunotherapy of Cancer, 2021
Regnase-1 + TGFBR2 Double KO Consistently Outperformed Other Combinations

Regnase-1 + TGFBR2 KO proved the most potent combo across multiple different tumor models and antigens

*CAKI-1 RCC xenograft*

- Maintenance of memory cell properties allows for greater expansion and anti-tumor activity

**T<sub>CM</sub>** phenotype maintained longer with Regnase-1 + TGFBR2 double KO
Regnase-1 and TGFBR2 KO Address Both Intrinsic and Extrinsic “Brakes” on T Cell Activity

Regnase-1 and TGFBR2 KO work synergistically to increase effector function in the presence of TME inhibitory signals like TGF-β while maintaining memory cell functional attributes.

Figure created using BioRender
Next-Gen Allogeneic CAR-T Candidates Build on Core Chassis

**Generation 2.0 allogeneic CAR T chassis:**

- **Regnase-1:** Removes intrinsic “brake” on T cell function
- **Increases functional persistence, cytokine secretion and sensitivity, effector function on tumors**
- **TGFBR2 KO:** Removes key extrinsic “brake” on T cell anti-tumor activity
- **Reduces TME inhibition of multiple CAR-T cell functions**

CTX112 and CTX131, our next-gen CD19 and CD70 targeting therapies, contain these additional edits (CTX131 also contains a CD70 locus knockout) – details in patent ID US 11,497,773
Prolonged Survival and Consistent Tumor Reduction Observed in CD19+ and CD70+ Malignancies In Vivo

CTX122 extends survival in Nalm6-Luc mice

CTX131 eliminates tumors in tumor rechallenge with ACHN (RCC)

Regnase-1 + TGFBR2 double KO outperforms either KO alone regardless of CAR construct or cancer model
A Single Dose of CTX131 Eliminates 3 Different Tumor Models in Succession Without Loss of Function

Tumor 1: NCI-H1975 (Lung)
Tumor 2: Rechallenge 1 with ACHN (RCC)
Tumor 3: Rechallenge 2 with Caki-1 (RCC)

Single dose CART

![Graphs showing tumor volume over days for each tumor model and treatment group](image-url)
Trials for CTX112 and CTX131 Follow Similar Protocols as Our CARBON and COBALT Trials

Standard lymphodepletion regimen of Flu 30mg/m^2 + Cy 500mg/m^2 for 3 days

<table>
<thead>
<tr>
<th>Candidate</th>
<th>NTC</th>
<th>Trial Name</th>
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<tr>
<td>CTX110</td>
<td>NCT04035434</td>
<td>A Safety and Efficacy Study Evaluating CTX110 in Subjects With Relapsed or Refractory B-Cell Malignancies (CARBON)</td>
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<tr>
<td>CTX112</td>
<td>NCT05643742</td>
<td>A Safety and Efficacy Study Evaluating CTX112 in Subjects With Relapsed or Refractory B-Cell Malignancies</td>
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<td>CTX130</td>
<td>NCT04502446</td>
<td>A Safety and Efficacy Study Evaluating CTX130 in Subjects With Relapsed or Refractory T or B Cell Malignancies (COBALT-LYM)</td>
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<tr>
<td>CTX131</td>
<td>NCT05795595</td>
<td>A Safety and Efficacy Study Evaluating CTX131 in Adult Subjects With Relapsed or Refractory Solid Tumors</td>
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Preclinical Data of Our Next-Gen Allo CAR T Candidates Supports Development for Hard-to-Treat Cancers

- Clinical data with CTX110 and CTX130 demonstrate that allogeneic CAR T efficacy and durable remissions do not require intense immune suppression or long-lived CAR T persistence.
- Regnase-1 + TGFBR2 double KO increases cell killing and functional persistence, provides resistance to environmental suppression, and preserves memory functions to enhance anti-tumor activity.
- Furthermore, the robustness and proliferation capacity of CAR T cells bearing these edits simplifies manufacturing and increases production capacity.
- Addition of these next-generation edits to our core chassis could enable allogeneic CAR T use in the most challenging patients and toughest indications, including solid tumors.
- We have advanced this next-generation CAR T chassis into the clinic with CTX112 and CTX131 for CD19+ and CD70+ malignancies, respectively.
Thank you to all the patients, families and investigators involved in our clinical trials!