CRISPR THERAPEUTICS

CRISPR Therapeutics Innovation Day

June 21, 2022

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Caution should be exercised when interpreting results from separate trials involving separate product candidates. There are differences in the clinical trial design, patient populations, and the product candidates themselves, and the results from the clinical trials of autologous products may have no interpretative value on our existing or future results.

Disclosures

Dr. Swaminathan P. Iyer

- Professor, Lead of the T Cell Lymphoma Program, Department of Lymphoma/Myeloma, Division of Cancer Medicine at The University of Texas MD Anderson Cancer Center
- Dr. Iyer receives research support from CRISPR Therapeutics, Merck & Co., Seagen, Rhizen, Acrotech Biopharma, Legend Biotech, Innate Pharma, AstraZeneca, Dren Bio, Yingli, and Secura Bio; participates in scientific advisory boards for Seagen, Yingli Pharma, and Secura Bio; and participates in BioCure Rx's and Targeted Oncology's speaker bureaus as a speaker

Dr. Sumanta Pal

- Professor in the Department of Medical Oncology & Therapeutics Research and the Co-Director of the Kidney Cancer Program at City of Hope
- Dr. Pal does not have relevant research disclosures

CRISPR Therapeutics Highlights

Leading gene editing company | Broad pipeline | Best-in-class platform and capabilities

Broad pipeline of *ex vivo* and *in vivo* programs across four franchises: hemoglobinopathies, immuno-oncology, regenerative medicine, and *in vivo* approaches

In position for first BLA/MAA filing for a CRISPR-edited product with exagamglogene autotemcel (exa-cel), formerly known as CTX001™, in β-thalassemia and sickle cell disease

Proof-of-concept for allogeneic CAR-T achieved with CTX110 and CTX130, with >100 patients dosed with CRISPR-edited CAR-T cells across 4 trials

Proven track record of execution with best in-class-class capabilities and state-of-the-art internal GMP manufacturing facility

Preeminent CRISPR technology platform focused on the innovation that matters for transformative medicines

Transforming Medicine Across Four Core Franchises

Hemoglobinopathies

Potential BLA/MAA filing for exa-cel in Q4 2022

Immuno-oncology

Smart-edited allogeneic immune cells for cancer

Regenerative Medicine

Edited, stem cell-derived beta cells for diabetes

In vivo

>10 programs using both AAV and LNP approaches

Platform (next-generation editing and delivery)

Presenters on Today's Call

CRISPR Therapeutics

Samarth Kulkarni, PhD
Chief Executive Officer

PK Morrow, MD
Chief Medical Officer

Jon Terrett, PhD
Head of Research

Ali Rezania, PhD
Head of Regenerative Medicine

Principal Investigators

Sumanta Pal, MD
Principal Investigator, COBALT-RCC
City of Hope

Swami Iyer, MD
Principal Investigator, COBALT-LYM
University of Texas MD Anderson Cancer Center

Today's Agenda

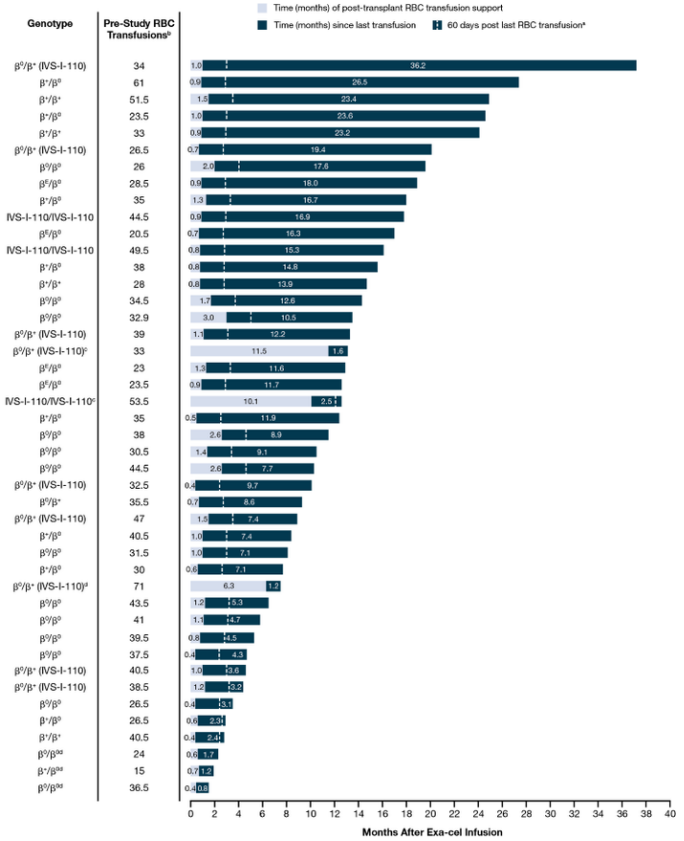
Introduction	**Samarth Kulkarni, PhD,** CEO
Hemoglobinopathies	**PK Morrow, MD,** CMO
Immuno-oncology	**PK Morrow, MD,** CMO
	Swami Iyer, MD, MD Anderson Cancer Center
	Sumanta Pal, MD, City of Hope
	Jon Terrett, PhD, Head of Research
	Q&A
Break (5 minutes)	
Regenerative medicine	**Ali Rezania, PhD,** Head of Regenerative Medicine
In vivo	**Jon Terrett, PhD,** Head of Research
Conclusion	**Samarth Kulkarni, PhD,** CEO
	Q&A

Hemoglobinopathies Strategy

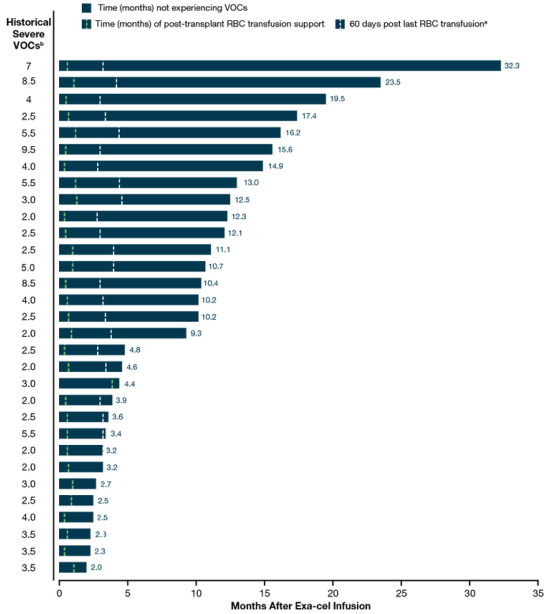
PK Morrow, MD, Chief Medical Officer

Exa-cel has a Functionally Curative Profile in SCD & TDT

β-thalassemia



Sickle cell disease

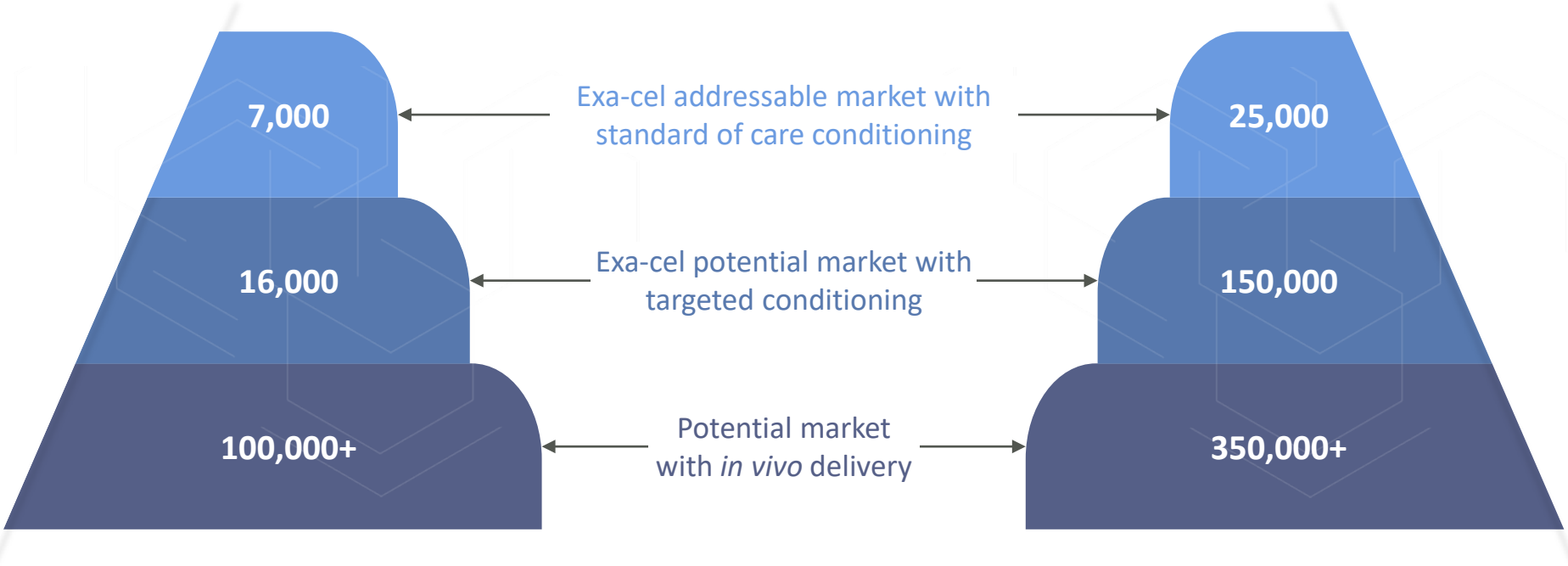


- **42/44 patients with transfusion-dependent thalassemia (TDT) stopped RBC transfusions** (duration from 0.8 to 36.2 months)
  - 2 patients had not yet stopped transfusions, but have 75% and 89% reductions in transfusion volume
- **31/31 patients with sickle cell disease (SCD) were VOC-free** (duration from 2.0 to 32.3 months)

RBC, red blood cell; VOC, vaso-occlusive crisis. Each row represents an individual patient
[a]Patients are evaluated for elimination of transfusions or VOCs starting 60 days after their last transfusion; [b]Number of transfusion units and pre-study severe VOCs annualized over 2 years; [c]Received RBC transfusions at or after data cut; [d]Patient stopped transfusions after data cut

Exa-cel has a Large Addressable Market

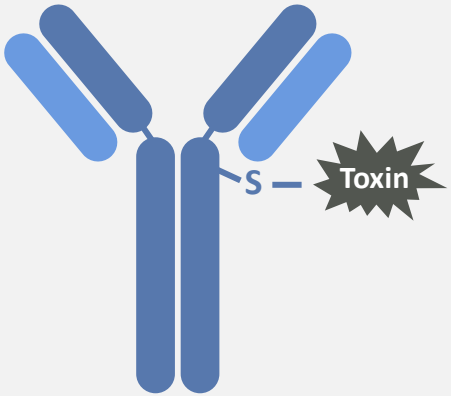
Opportunity to broaden market via innovation in conditioning and delivery



Advancing an Internal Program in Targeted Conditioning

Attributes of an optimal targeted conditioning agent

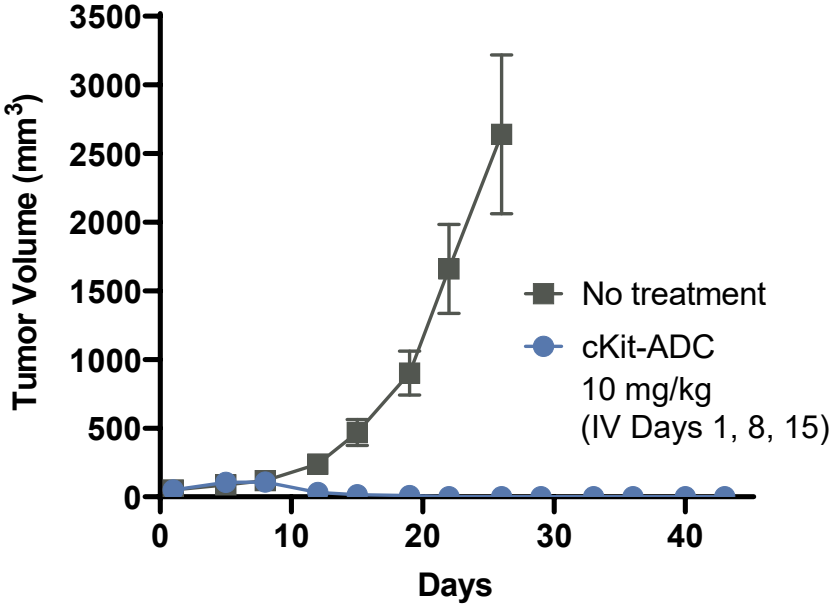
Differentiated cKit ADC approach



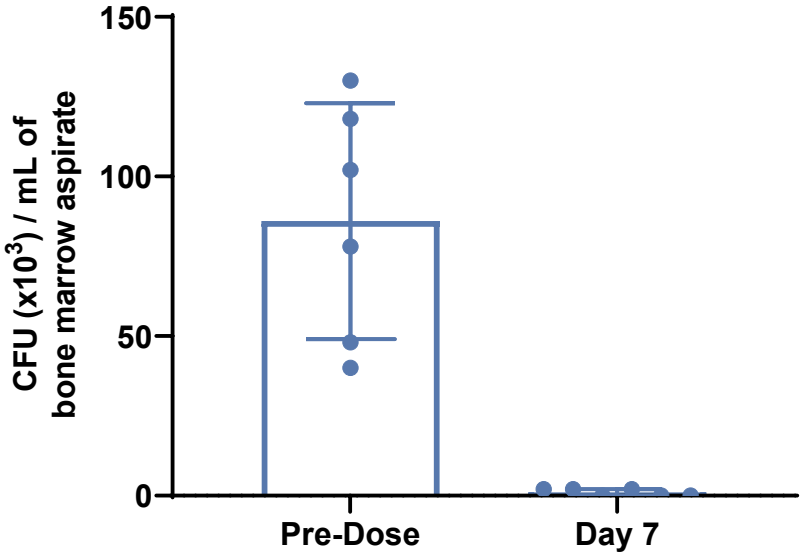
- *Best-in-class cKit mAb*
- *Well-validated toxin with HSC activity*
- *Extensive ADC development expertise within CRISPR Therapeutics*

Our cKit-ADC has High Potency with Limited Toxicity in NHPs

cKit-ADC eliminates Kasumi-1 AML xenograft tumor in mice

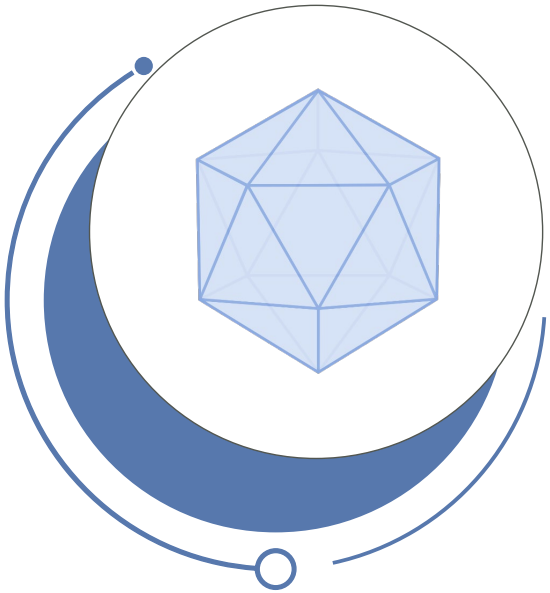


Single 13 mg/kg dose of cKit-ADC depletes functional HSCs in non-human primates

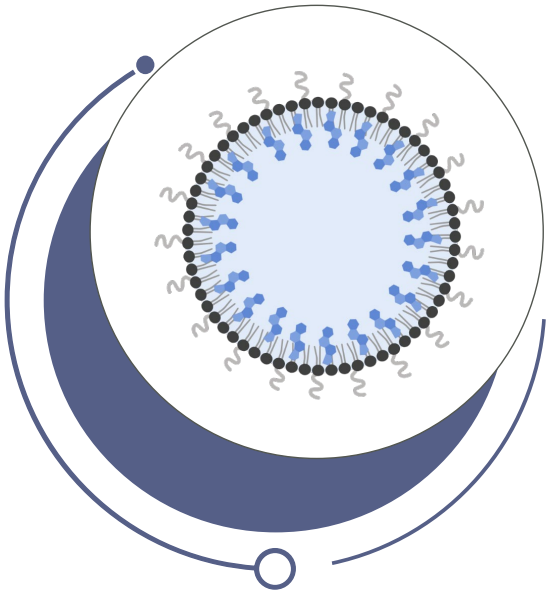


No clinically significant toxicities observed across all doses evaluated thus far, up to 30 mg/kg in NHPs and mice

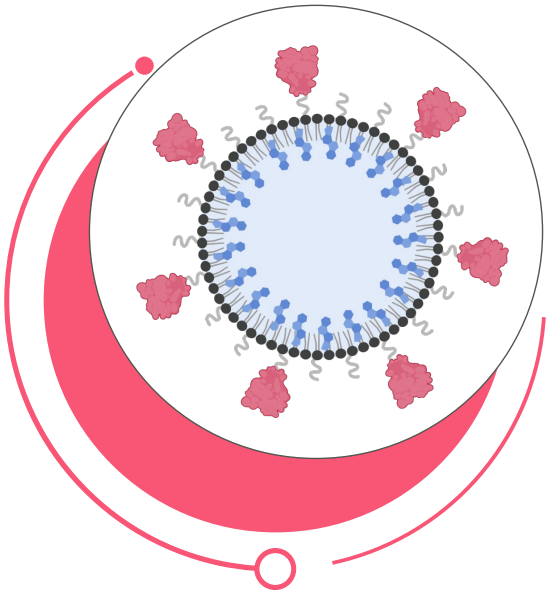
Progressing Multiple Approaches to *In Vivo* HSC Editing



AAV



LNP

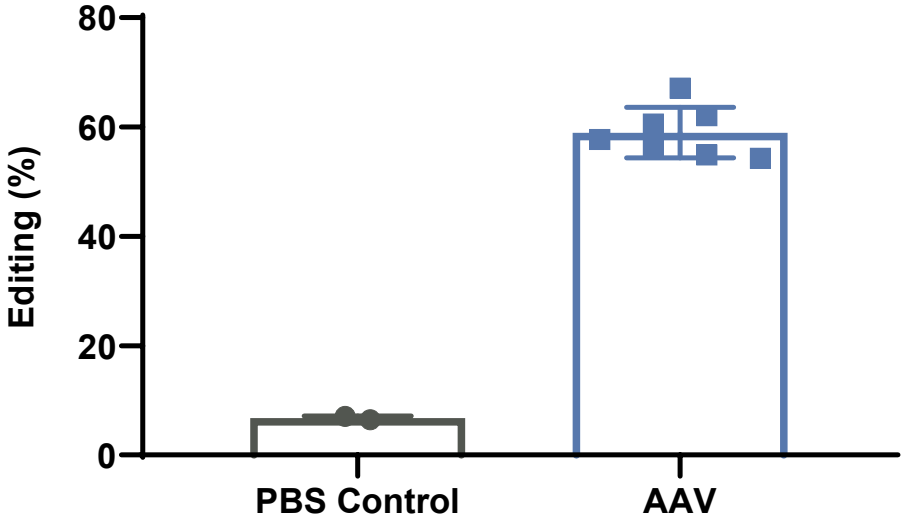


Targeted LNP

AAV: Adeno-associated virus; LNP: Lipid nanoparticle

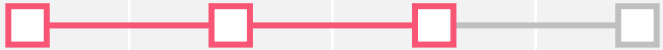
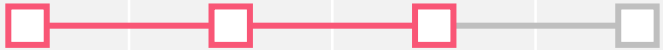
POC Established for *In Vivo* Editing of HSCs with AAV

~60% editing of CD34+/CD90+ HSC population in humanized mice
Dual AAV vectors to deliver Cas9 and gRNA

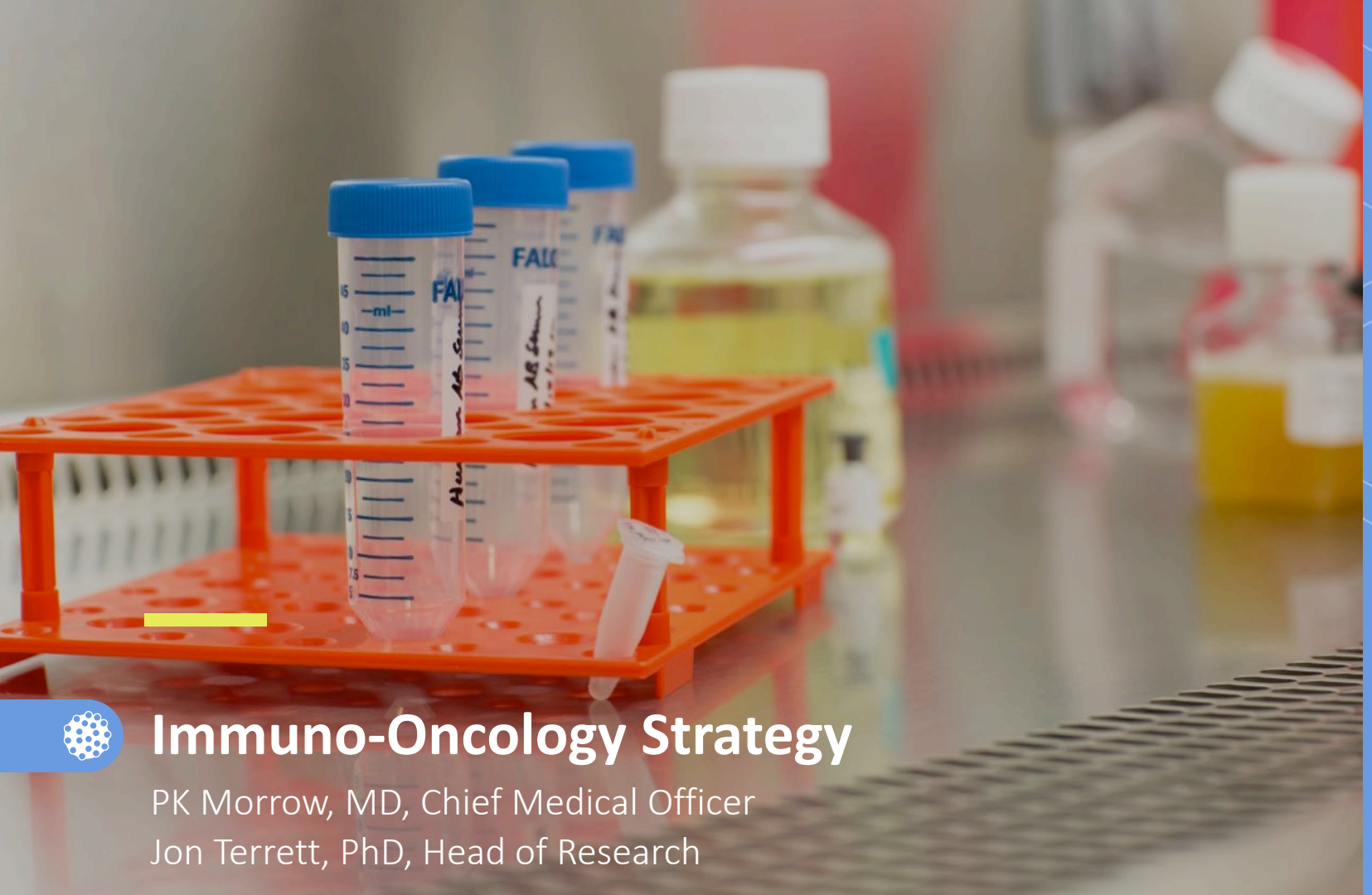


Additionally, preservation of editing in secondary engraftment studies confirms editing of true long-term HSCs

Hemoglobinopathies Pipeline

Program	Research	IND-enabling	Clinical	Marketed	Status	Partner	Structure
Exa-cel: β-thalassemia					Fully enrolled	VERTEX	Collaboration
Exa-cel: Sickle cell disease (SCD)					Fully enrolled		
Next-generation conditioning							Wholly-owned[1]
In vivo editing of HSCs							

1 Collaboration with Vertex for applications in β-thalassemia and SCD



Immuno-Oncology Strategy

PK Morrow, MD, Chief Medical Officer
Jon Terrett, PhD, Head of Research

Significant Progress in the CTX110 Program

Moving into late-stage development

RMAT kickoff discussion held to align on key clinical and CMC questions

Advancing consolidation regimen

15+ patients dosed in consolidation cohorts

Addressing a strong unmet need

Up to 30% of eligible patients unable to be infused with autologous CAR-T

Sources: Neelapu, et al. (2017). *New England Journal of Medicine.* 377:2531-2544. Schuster, et al. (2019). *New England Journal of Medicine.* 380:45-56. Abramson, et al. (2020). *Lancet.* 396(10254):839-852.

Path Forward for BCMA-Directed CAR-T

Completed CTX120 dose escalation up to Dose Level (DL) 4; 1 subject treated at DL5

No dose limiting toxicities (DLT) observed, including no CRS above Grade 2 and no ICANS or GvHD, of any grade

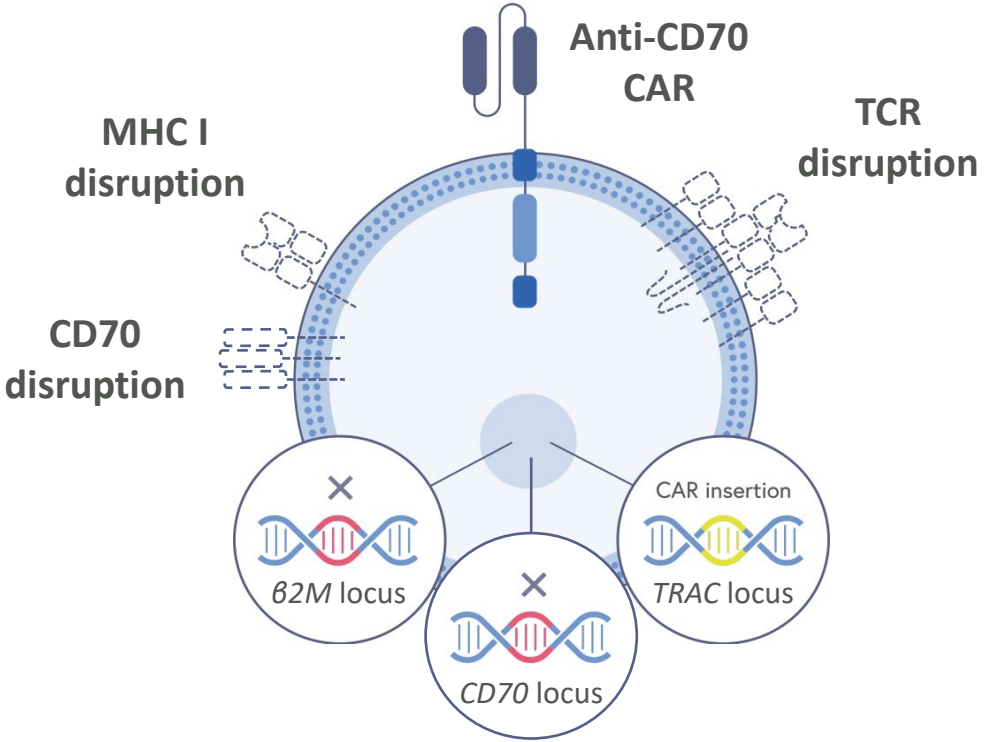
Dose dependent responses seen, but aiming to improve efficacy given competitive context

Pivot to next-generation allogeneic CAR-T program for multiple myeloma (CTX121)

Further data disclosure in a future scientific publication

CTX130 – New Biology, Advanced Engineering

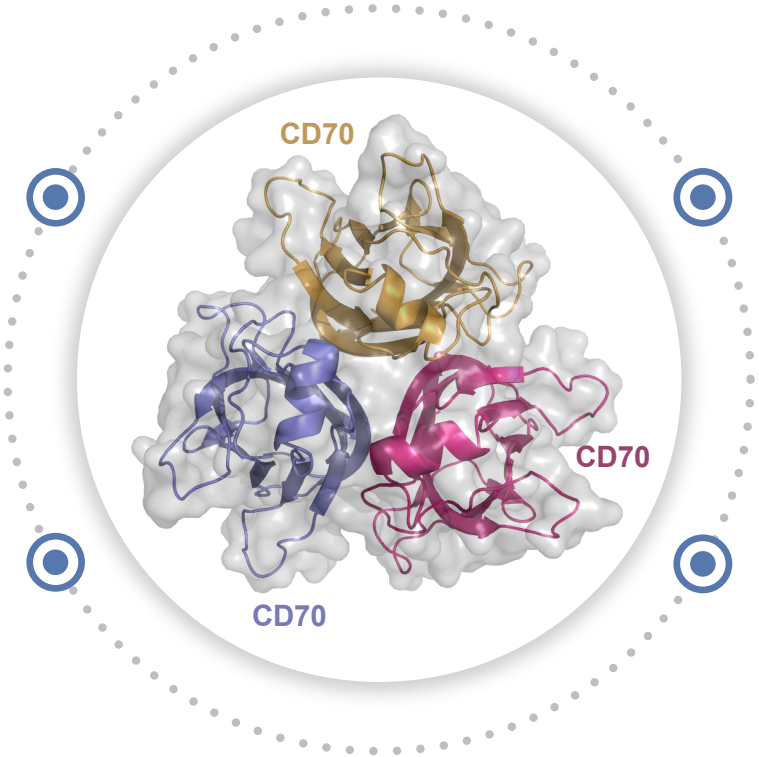
CTX130 Construct



CD70 – Novel Target with Expression in Multiple Cancers

Member of TNF ligand family involved in T cell activation via cognate receptor CD27

High expression in multiple hematological malignancies, e.g., T cell lymphoma (TCL), DLBCL, and AML



Significant expression in solid tumors, including clear cell renal cell carcinoma (ccRCC), glioblastoma, pancreatic, lung, ovarian, head and neck, and esophageal cancers

Minimal expression on healthy tissues – viability established in clinical studies with ADCs

AML, acute myeloid leukemia; DLBCL, diffuse large B cell lymphoma

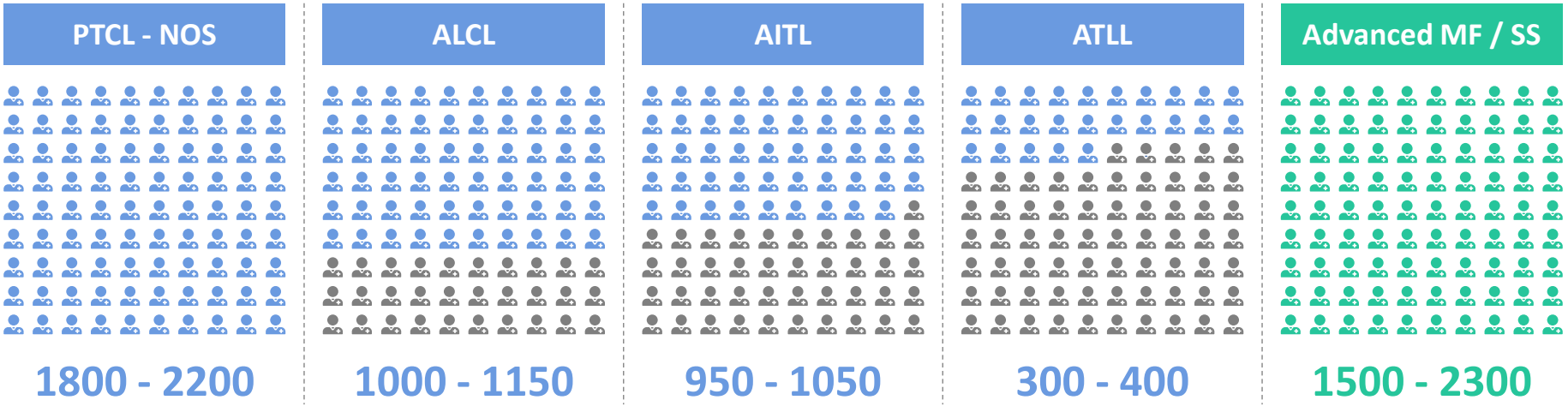
Sources: Liu, et al. *J Biol Chem.* 2021;297(4):101102. Wajant. *Expert Opin Ther Targets*. 2016;20;959-973. Marques-Piubelli, et al. *Histopathology*. 2022 Apr 26. doi:10.1111/his.14670. Online ahead of print.

T Cell Lymphoma Represents a Large Unmet Need and Significant Opportunity

Annual U.S. + EU5 incidence of patients with CD70 expression by indication subtype

Peripheral T Cell Lymphomas

Cutaneous T Cell Lymphomas



Total annual U.S. + EU5 addressable market is 5000 – 7000 patients per year

PTCL-NOS: Peripheral T Cell Lymphoma – Not Otherwise Specified; ALCL: Anaplastic Large Cell Lymphoma; AITL: Angioimmunoblastic T cell Lyphoma; ATLL: Adult T cell Leukemia/Lymphoma; MF / SS: Mycosis Fungoides / Sezary Syndrome

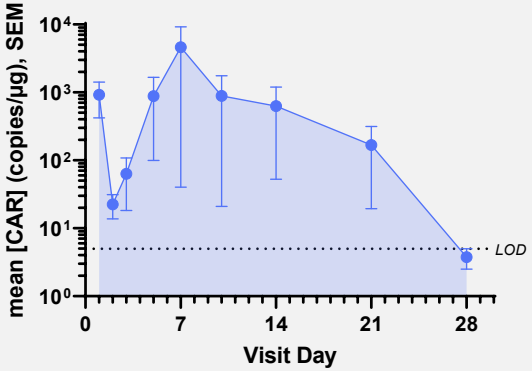
Sources: SEER database 2021; KOL analysis; Office of National Statistics 2021; Eurostat 2021

COBALT-LYM Patient Demographics and Pharmacokinetics

Patient characteristics, *All Dose Levels n = 18*	
Age, median years (range)	65 (39 – 78)
ECOG PS at screening, n (%)	
0	8 (44)
1	10 (56)
Prior lines of therapy, median n (range)	4 (1 – 8)
TCL subtype, n (%)	
PTCL	8 (44)
AITL	3 (17)
ALCL	1 (6)
ATLL	3 (17)
PTCL - NOS	1 (6)
CTCL (MF, SS, tMF)	10 (56)
Skin involvement, n (%)	12 (67)
Blood involvement, n (%)	6 (33)
Bone marrow involvement, n (%)	4 (22)
CD70 expression level, median % (range)	90 (20 – 100)
Second CTX130 infusion received, n (%)	5 (28)

Pharmacokinetics, *All Dose Levels n = 18*	
Peak expansion concentration (C_{max})*†, geometric mean copies/µg (range)	80.9 (<4.9 – 61,349.8)
Time to peak expansion (T_{max})†, median days (range)	8.5 (5 – 14)

Peak expansion concentration (C_{max})*† at DL4, n=5[1]



* For summary statistics of C_{max}, values below the limit of detection (LOD) were imputed as half the LOD and values below the limit of quantification (LOQ) were imputed as (LOQ+LOD)/2.
† From Screening to D28 post infusion. [1] Includes first infusions only.

Data cutoff date: 26 April 2022

Presented at the European Hematology Association Annual Meeting. 11 June 2022

CTX130 Safety Profile

Adverse Events of Interest, N (%)

	DL1 $3x10^7$ N=4		DL2 $1x10^8$ N=4		DL3 $3x10^8$ N=5		DL4 $9x10^8$ N=5		DL≥3 N=10	
	Gr 1-2	Gr ≥3	Gr 1-2	Gr ≥3	Gr 1-2	Gr ≥3	Gr 1-2	Gr ≥3	Gr 1-2	Gr ≥3
CRS	1 (25)	-	1 (25)	-	4 (80)	-	4 (80)	-	**8 (80)**	-
ICANS	-	-	-	-	3 (60)	-	-	-	**3 (30)**	-
GvHD	-	-	-	-	-	-	-	-	-	-
Infections	2 (50)	1 (25)	-	1 (25)	2 (40)	1 (20)	1 (20)	1 (20)	**3 (30)**	**2 (20)**

All events listed in table are treatment-emergent adverse events. CRS, cytokine release syndrome; DLT, dose-limiting toxicity; EBV, Epstein-Barr virus; Gr, grade; GvHD, graft versus host disease; HLH, hemophagocytic lymphohistiocytosis; ICANS, immune effector cell associated neurotoxicity syndrome; LDC, lymphodepleting chemotherapy; SAE, serious adverse events; TLS, tumor lysis syndrome

Data cutoff date: 26 April 2022

- Acceptable safety profile across all DLs: no DLTs or instances of TLS with LDC or CTX130
- Treatment-emergent (TE) SAEs occurred in 10/18 (56%) patients and included Gr ≥3 infections (n=4, 22%), Gr 1-2 tumor hemorrhage, Gr ≥3 syncope, Gr ≥3 presyncope, Gr ≥3 HLH, Gr ≥3 drug eruption, and Gr 1-2 ligament sprain (n=1 each, 6%). With exception of one Gr 3 infection, all other TE SAEs were not found to be related to CTX130
- There was a sudden death in 1 patient with William's syndrome in the context of a lung infection, deemed unrelated to CTX130
- Three cancers were diagnosed in patients with CTCL post treatment: 1 patient had EBV-associated lymphoma which resolved and a squamous cell carcinoma, 1 patient had invasive ductal breast carcinoma which was resected and cured. These were deemed unrelated to CTX130

Presented at the European Hematology Association Annual Meeting. 11 June 2022

70% ORR and 30% CR Rate at DL3 and Above

Best overall response, n (%)

Cell dose (CAR+ T cells)	DL1 $3x10^7$ N=4	DL2 $1x10^8$ N=4	DL3 $3x10^8$ N=5	DL4 $9x10^8$ N=5	DL≥3 N=10
Overall Response Rate (ORR)	2 (50)	0	3 (60)	4 (80)	**7 (70)**
CR	1 (25)	0	2 (40)*	1 (20)	**3 (30)**
PR	1 (25)	0	1 (20)	3 (60)	**4 (40)**
Disease Control Rate (DCR = CR + PR + SD)	3 (75)	1 (25)	5 (100)	4 (80)	**9 (90)**

	PTCL		CTCL	
	DL≥3 N=5	Total N=8	DL≥3 N=5	Total N=10
ORR	4 (80)	5 (63)	3 (60)	4 (40)
CR	2 (40)	3 (38)	1 (20)	1 (10)
PR	2 (40)	2 (25)	2 (40)	3 (30)
DCR	4 (80)	5 (63)	5 (100)	8 (80)

*1 patient in DL3 who initially achieved a PR was re-infused at DL4 following a change to SD and achieved a CR at DL4.

CAR, chimeric antigen receptor; CR, complete response; CTCL, cutaneous T cell lymphoma; DCR, disease control rate; DL, dose level; ORR, overall response rate; PR, partial response; PTCL, peripheral T cell lymphoma; SD, stable disease

Data cutoff date: 26 April 2022

Presented at the European Hematology Association Annual Meeting. 11 June 2022

CTCL Responses Observed Across All Compartments

*Day 7 assessment; †Initially unconfirmed CR, later confirmed to be PR by mSWAT and biopsy.
CR, complete response; CTCL, cutaneous T cell lymphoma; DL, dose level; PD, progressive disease; PR, partial response; SD, stable disease

Data cutoff date: 26 April 2022

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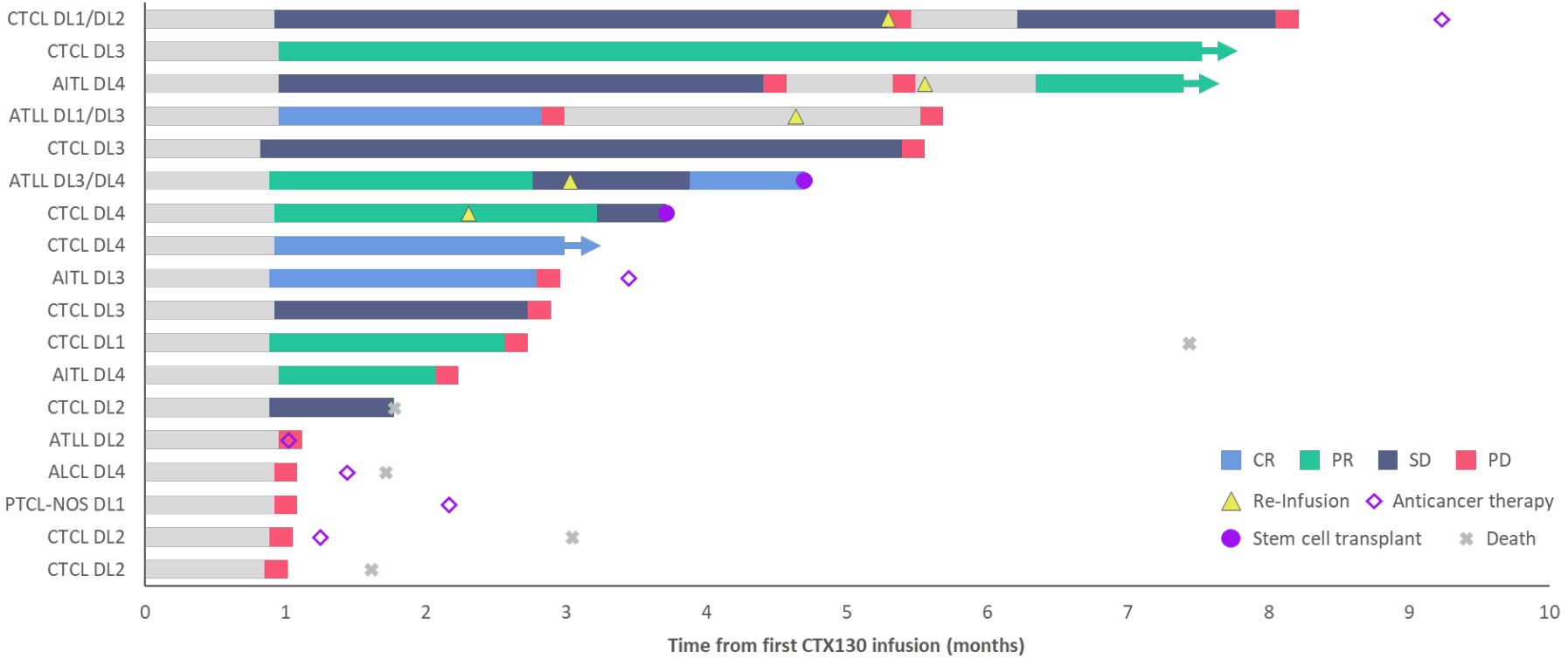
Clinically Meaningful Responses with CTX130



AITL, angioimmunoblastic T cell lymphoma; ALCL, anaplastic large cell lymphoma; ATLL, adult T cell leukemia/lymphoma; CR, complete response; CTCL, cutaneous T cell lymphoma; DL, dose level; PD, progressive disease; PR, partial response; PTCL-NOS, peripheral T cell lymphoma not otherwise specified; SD, stable disease

Data cutoff date: 26 April 2022

Presented at the European Hematology Association Annual Meeting. 11 June 2022

Opportunity to Change the Paradigm in T Cell Lymphomas

Opportunity for CTX130 in TCL

- Significant unmet need with limited treatment options in both PTCL & CTCL
- CTX130 has demonstrated high ORR with multi-compartment response and a tolerable safety profile
- Re-dosing can deepen responses and further improve durability
- Given high unmet need, potential path to accelerated approval

CTX130 has higher response rates than existing therapies

CTCL	CTX130 DL ≥ 3 *N = 5*	Vorinostat *N = 74*	Mogamulizumab *N = 186*	Romidepsin *N = 96*	Brentuximab vedotin (CD30+) *N = 48*
Overall response rate (ORR), N (%)	3 (60%)	22 (30%)	52 (28%)	33 (34%)	31 (65%)[2]
Complete response (CR), N (%)	1 (20%)	1 (1%)	5 (3%)	6 (6%)	5 (10%)

PTCL	CTX130 DL ≥ 3 *N = 5*	Pralatrexate *N = 109*	Belinostat *N = 120*	Brentuximab vedotin (CD30+ ALCL only) *N = 58*
Overall response rate (ORR), N (%)	4 (80%)	32 (29%)	31 (26%)	50 (86%)
Complete response (CR), N (%)	2 (40%)	12 (11%)	13 (11%)	33 (57%)

Sources: Olsen, et al. *Journal of Clinical Oncology*, 2007;25(21):3109–3115. Kim, et al. *Lancet Oncology.* 2018;19:1192-204. Whittaker, et al. *Journal of Clinical Oncology.* 2010;28(29):4485-91. O'Connor, et al. *Journal of Clinical Oncology.* 2011;29(9). O'Connor, et al. *Journal of Clinical Oncology.* 2015;33(23).

RCC has Large Unmet Need and Significant Addressable Population

Renal Cell Carcinoma (RCC)

Significant worldwide burden

50K US  45K EU5

Annual incidence

High morbidity and mortality

 18%

5-year survival for stage IV

Poor response rates to current therapies

 40%

Primary refractory

High potential opportunity

 80%

CD70 expression in RCC

Sources: SEER; Globocan 2020; WCRFI; ZfKD; Cancer Research UK; Epidemiology of Renal Cell Carcinoma. Powles. *Lancet Oncology*. 2020;21:1563-73. Adam, et al. *Br J of Cancer*. 2006;95(3):298-306.

Patient Baseline Characteristics and Safety in COBALT-RCC

Patient characteristics *All Dose Levels, N=14*	
Age, median years (range)	64.5 (51 – 77)
Male, n (%)	12 (86)
Stage IV at screening, n (%)	14 (100)
Prior treatments, median n (range)	3 (1 – 6)
CD70 expression level, median % (range)	100 (1 – 100)

Adverse Events of Interest, N (%)
All Dose Levels, N=14

- **Acceptable safety profile across all dose levels to date, including no DLTs**
- No instances of tumor lysis syndrome, infusion reactions, HLH, ICANS, GvHD or secondary malignancies occurred
- 7 (50%) patients had Gr 1-2 CRS; no Gr ≥ 3 CRS events
- 3 patients with SAEs related to CTX130; all were CRS events
- 3 patients with SAEs of infections, all found to be unrelated to CTX130, including a pneumonia with Gr 5 dyspnea resulting in death

CRS, cytokine release syndrome; DLT, dose-limiting toxicity; Gr, grade; GvHD, graft versus host disease; HLH, hemophagocytic lymphohistiocytosis; ICANS, immune effector cell associated neurotoxicity syndrome; SAE, serious adverse events
Data cutoff: May 2022

Evidence of Activity for CTX130 in RCC – a First for Allogeneic Cell Therapy in Solid Tumors

CTX130 shows promising potential disease control in COBALT-RCC

Cell dose (CAR+ T cells)	DL1 $3x10^7$ N=3	DL2 $1x10^8$ N=3	DL3 $3x10^8$ N=4	DL4 $9x10^8$ N=4	Total N=14
Overall response rate	1 (33)	0	0	0	**1 (7)**
Stable disease	2 (67)	2 (67)	2 (50)	4 (100)	**10 (71)**
Disease Control Rate (DCR = CR + PR + SD)	3 (100)	2 (67)	2 (50)	4 (100)	**11 (79)**

- One patient with complete response has maintained their CR through their most recent visit at M18
- Typical PK seen with peak time to expansion at a median of D10 and peak concentration of ~3500 copies/µg
- Encouraging results underscore the potential of further increasing potency

Case Study | Durable Complete Response in RCC with CTX130

Subject Overview

Patient profile

- 64-year-old male with clear cell RCC diagnosed in 2017
- 1 prior line of therapy with cabozantinib and atezolizumab
- Relapsed after PR with lesions in the lung and pleura
- CD70+ expression: 100% at baseline

Efficacy

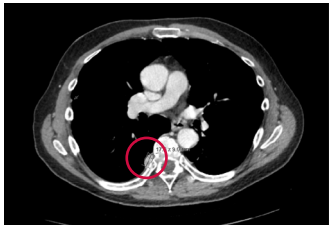
- PR at D42 after a single infusion of $3x10^7$ CAR+ T cells
- CR at M3 and remains in CR at M18

Safety

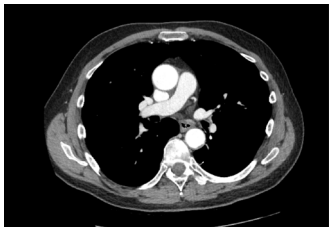
- Only Gr 1-2 adverse events
- No AEs considered related to CTX130

Deepening of response over time

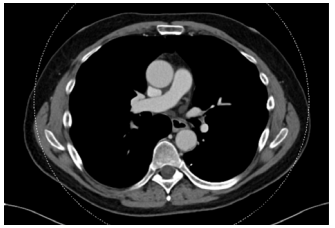
Screening



Day 42



Month 18



Executing on Our Immuno-oncology Strategy

Validate

Our allogeneic platform with proven targets

- **Proof of concept with CTX110,** showing durable complete remissions with allogeneic CAR-T

Expand

From hematologic cancers into solid tumors

- **Promising data with CTX130** in TCL
- **1st activity in solid tumors** with allogeneic CAR-T

Unlock

The full potential of I/O cell therapy with next-gen edits and targets

- 2nd-generation programs with **novel potency edits**
- **Novel targets**, including via collaborations with top cancer centers

Second-Generation Products Focus on Potency

Autologous and allogeneic CAR-T trial data suggest initial depth of response, rather than CAR-T persistence, matters most for durability

CTX110

Durable complete responses after a single dose

Yescarta

Patients have durable responses even though CAR-T cells are undetectable by 3 months

Early MRD negativity

Correlated with durable responses

Carvykti

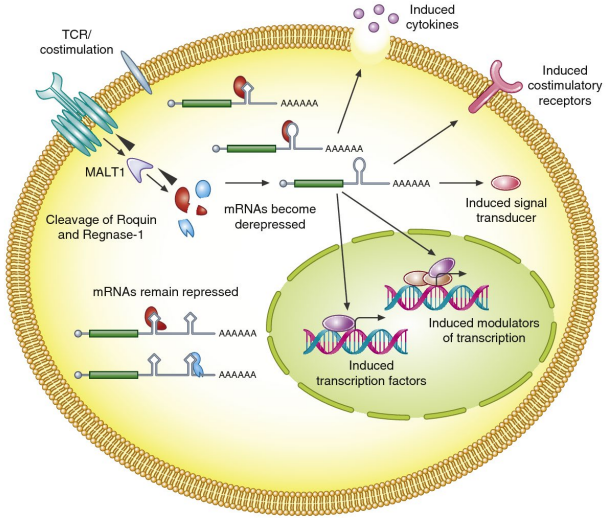
mDOR of 21.8 months even though 79% of patients have undetectable CAR-T cells by 6 months

Sources: Frank, et al. *J Clin Oncol*. 2021 Sep 20;39(27):3034-43. Hay, et al. *Blood*. 2019;133 (15):1652–63. Locke, et al. *Lancet Oncol*. 2019 Jan;20(1):31-42. Locke, et al. *Blood Adv*. 2020 Oct 13;4(19):4898-4911. Berdeja, et al. *Lancet*. 2021 Jul 24;398(10297):314-24. CARVYKTI package insert. CTX110 data

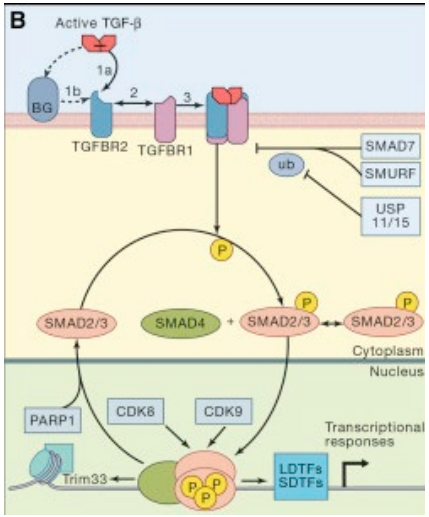
Optimal Potency Edits Identified Via Systematic Screening

High-throughput CRISPR screening identified synergistic potency edits

Regnase-1 KO: *removes intrinsic "brake" on T cell function*



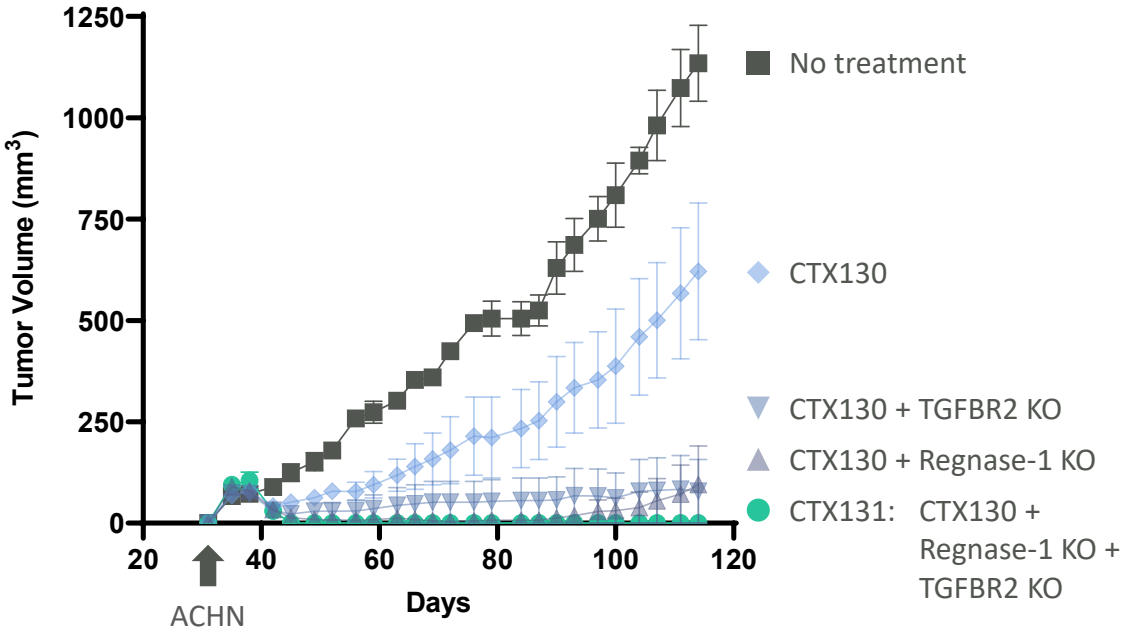
TGFBR2 KO: *removes key extrinsic "brake" on T cell anti-tumor activity*



Sources: Jeltsch & Heissmeyer. *Curr Opin Immunol*. 2016 Apr;39:127-35; Batlle & Massague. *Immunity*. 2019 Apr 16;50(4):924-940

Regnase-1 and TGFBR2 Edits Show Synergistic Activity

Only Regnase-1 + TGFBR2 KO CAR-T cells can eliminate a difficult tumor re-challenge model

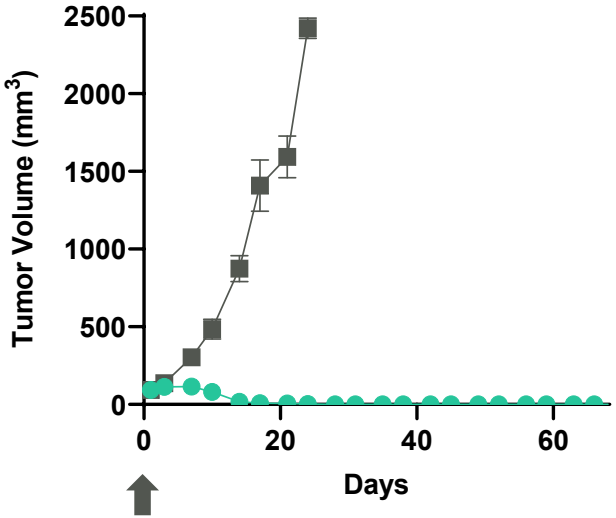


KO: Knockout

CTX131 Shows Enhanced Potency

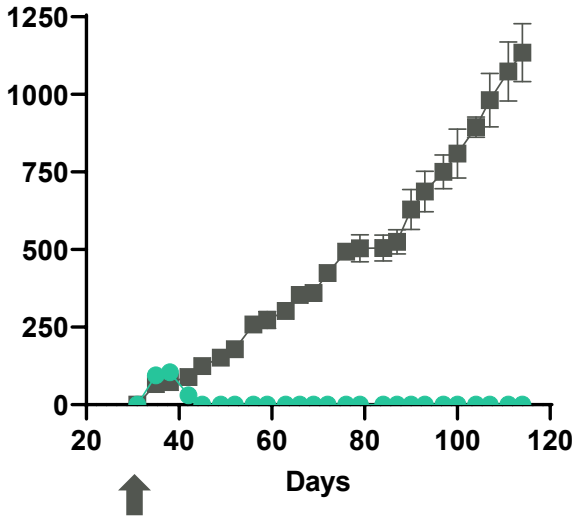
CTX131 eliminates three different xenograft tumor models in succession without exhaustion

Tumor 1: *NCI-H1975 (Lung)*



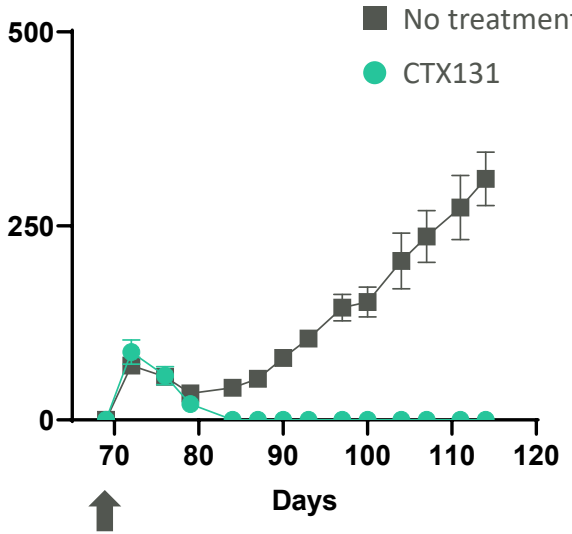
Single dose CAR-T

Tumor 2: *Rechallenge 1 with ACHN (RCC)*



ACHN

Tumor 3: *Rechallenge 2 with Caki-1 (RCC)*

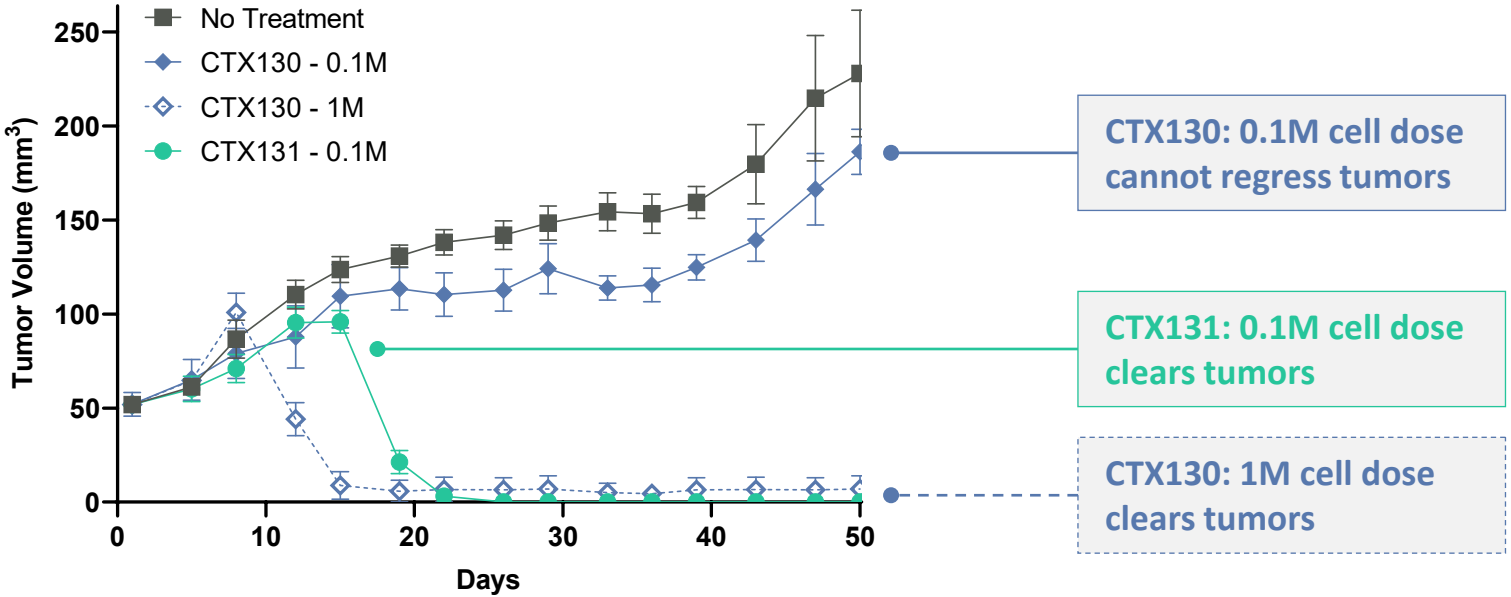


Caki-1

n=5 mice per group

2nd-Gen Edits Enhance Potency ~10x Over 1st-Gen

Superior performance of CTX131 over CTX130 in an RCC (Caki-2) xenograft model

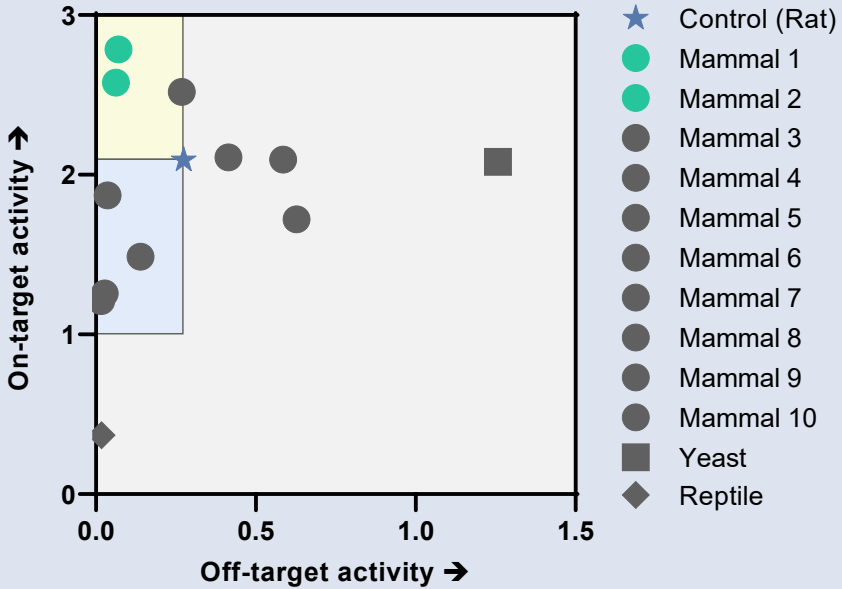


We expect to advance two next-generation constructs to IND by end of 2022: CTX131 and CTX112 targeting CD70 and CD19, respectively

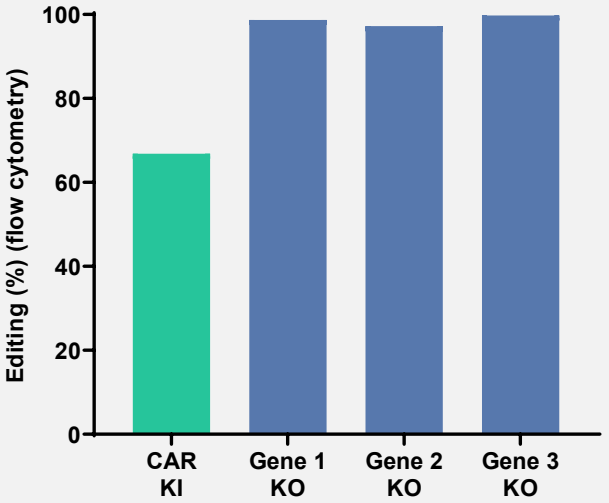
Developing Base Editors for CAR-T Programs with 7+ Edits

Large-scale screen to identify proprietary base editor to enable 7+ edits for 3rd-generation CAR-T

Promising new APOBEC1 candidates for cytosine base editors identified from natural world screening



High base editing rates achieved to generate multiplexed CAR-T cells



Building on Our Success in Advancing Novel Targets

CD70, our first novel CAR-T target for lymphomas and solid tumors, validated through our COBALT trials

We have prioritized additional novel targets with the potential to address a variety of cancers, pairing them with our next-generation edits

We're accelerating clinical validation of these targets with autologous and allogeneic platforms through collaborations with leading cancer centers

Collaborations with Top Cancer Centers on New Targets

Clinical trial to begin in next 12 months

- **First-in-human trial for autologous CAR-T therapy targeting CD83**
- **CD83:** Expressed on certain cancers and activated T cells – potential in AML and other oncology and autoimmune indications
- Additional research in collaboration with the Masonic Cancer Center, University of Minnesota

IND-enabling studies to begin this year

- **Initial trial for gene-edited, autologous CAR-T therapy targeting GPC3**
- **GPC3:** Solid tumor target for hepatocellular carcinoma (HCC) with limited expression in healthy tissues – potency edits have potential to enhance CAR-T activity against solid tumors

Cancer centers conduct viral vector manufacturing, cell manufacturing, and Phase I trial
CRISPR retains commercial rights

Robust Early and Late Stage I/O Pipeline

		Program	Generation	Research	IND-enabling	Clinical	Marketed	Status	Partner	Structure
Allogeneic	CD19	CTX110	1					Enrolling		Wholly owned
		CTX112	2							Wholly owned
	CD70	CTX130	1					Enrolling		Wholly owned
		CTX131	2							Wholly owned
		NK-CD70 (CAR-NK)	2						nkarta THERAPEUTICS	Collaboration
	Other targets	CTX121 (anti-BCMA)	2							Wholly owned
		Other CAR-Ts	2							Wholly owned
Autologous	Novel targets	CD83	1						MOFFITT CANCER CENTER	Collaboration[1]
		GPC3	2						ROSWELL PARK	Collaboration[1]

1 CRISPR retains commercial rights

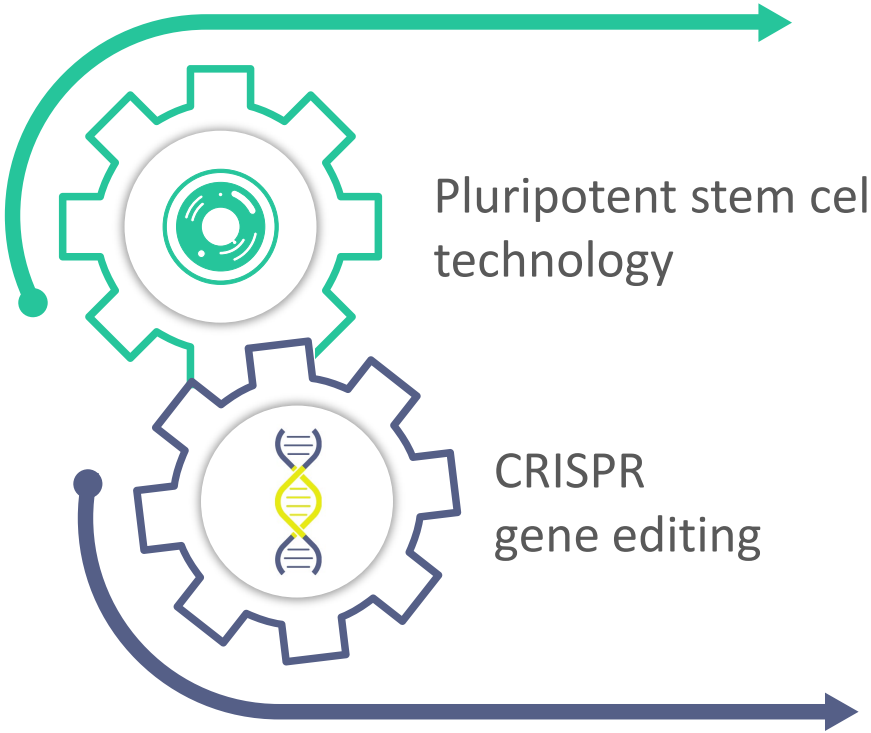
Questions

Break

Regenerative Medicine Strategy

Ali Rezania, PhD, Head of Regenerative Medicine

Combining Breakthroughs in Gene Editing and Stem Cells



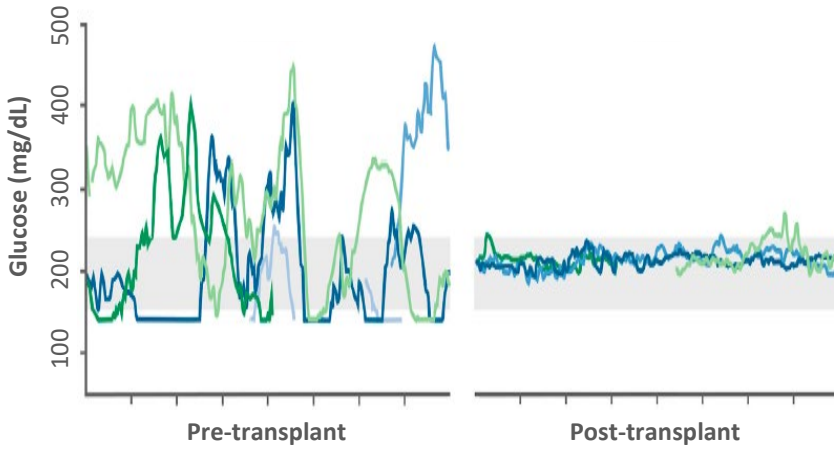
Pluripotent stem cell technology

CRISPR gene editing

Enables a new class of cell replacement therapies for both rare and common diseases

Potential Functional Cure for T1D via Beta Cell Replacement

Cadaveric islet transplant has curative efficacy in T1D



Not scalable due to scarcity of islet tissue

Requires chronic immunosuppression

Gene edited stem cells can enable broad applicability

Off-the-shelf, pluripotent stem cell-derived **scalable source of cells**

Multiplex genome editing to **avoid need for long-term immunosuppression and improve fitness and functionality**

First in the clinic with a gene-edited cell replacement approach for T1D

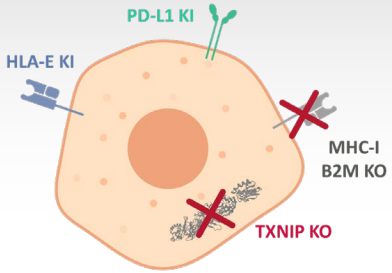
Source: Pepper, et al. *Current Opin Organ Transplant.* 2018;23(4):428-439. Moassesfar, et al. *Am J Transplant.* 2016;16(2):518-26. Latres, et al. *Cell Metab.* 2019; 29(3):545-563. Schuetz, et al. *Current Transplant Rep.* 2016; 3(3):254-263.

Multi-staged Product Strategy

Perforated Device Approach
- Progenitor cells (stage 4)
- Retrievable, enabling broader initial patient population

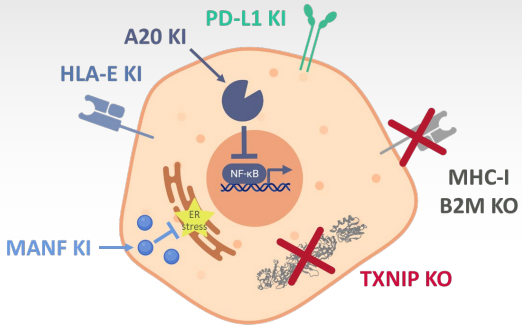
Deviceless approach
- Immature β-cells (stage 6)
- Portal vein injection

210



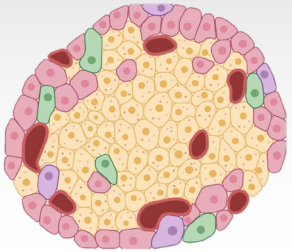
- Entered clinic Nov 2021
- Safety and immune evasion
- Informs 211 trial design

211



- Two additional edits to promote cell survival
- CTA filing planned for 2H22

212

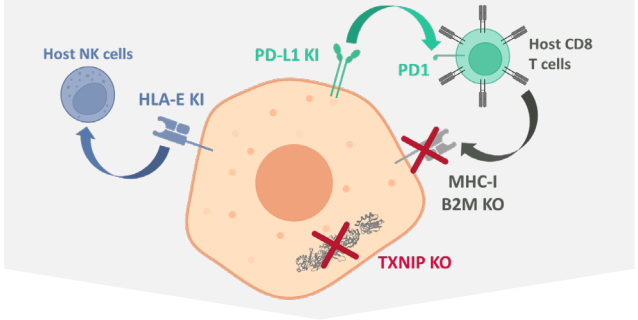


- Unencapsulated, stage 6 cell aggregates containing additional edits beyond 211
- Research stage program

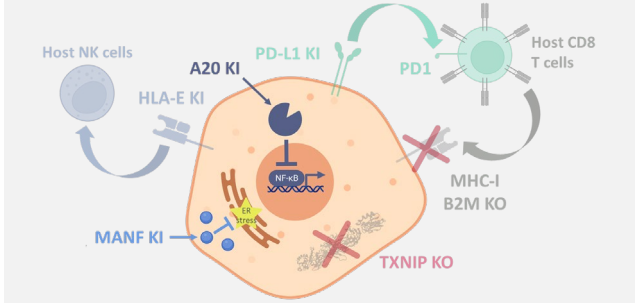
VCTX211 – Further Optimized for Cell Fitness

VCTX211 has 2 gene KOs and 4 insertions to improve functionality

VCTX210



VCTX211



Immune evasion

- **MHC-I KO** eliminates T cell mediated rejection
- **PD-L1 KI** reduces immune rejection, particularly from T cells
- **HLA-E KI** further reduces immune rejection, particularly from NK cells

Cell fitness

- **Thioredoxin interacting protein (TXNIP) KO** protects from oxidative and ER stress

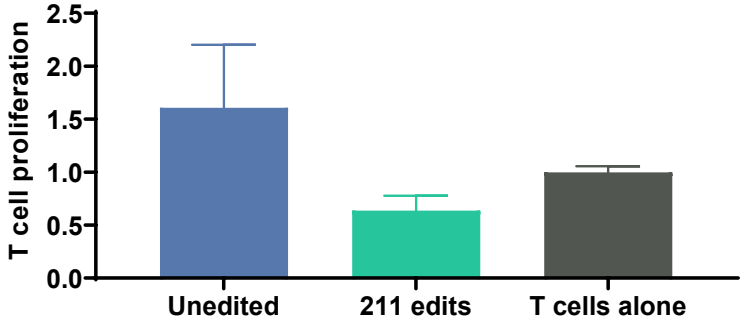
+

- **A20 (TNFAIP3) KI** induces graft acceptance and protection from cytokine induced apoptosis
- **MANF KI** enhances β cell proliferation and protection against inflammatory stress

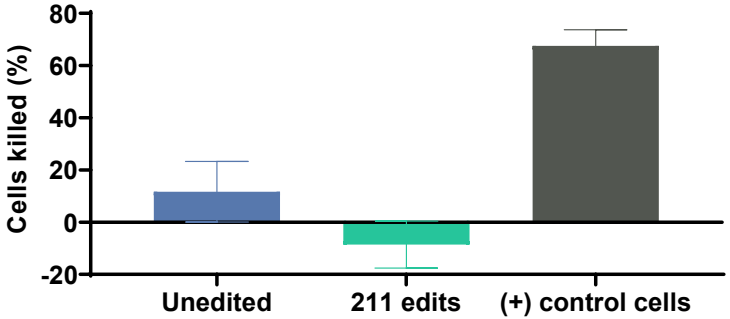
Sources: Qian, et al. *Immunology*. 1996; 88(1):124-9. Gornalusse, et al. *Nat Biotechnology.* 2017;35(8):765-72. El Khatib, et al. *Gene Therapy*. 2015;22(5):430-8. Chen, et al. *FASEB J.* 2008;22(10):3581-94. Shalev. *Biochem Soc Trans*. 2008;36(5):963-5. Lindahl, et al. *Cell Rep.* 2014;24(7):366-75. Zammit, et al. *JCI Insight.* 2019;4(21).

Edited Cells Evade Immunity *In Vitro* and *In Vivo*

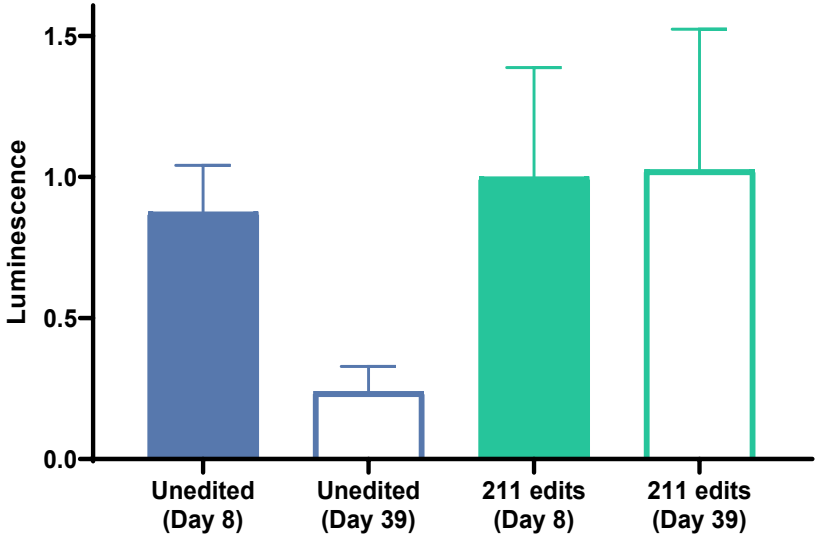
Adaptive – T cells do not respond to 211 cells *in vitro*



Innate – 211 cells resist NK attack *in vitro*



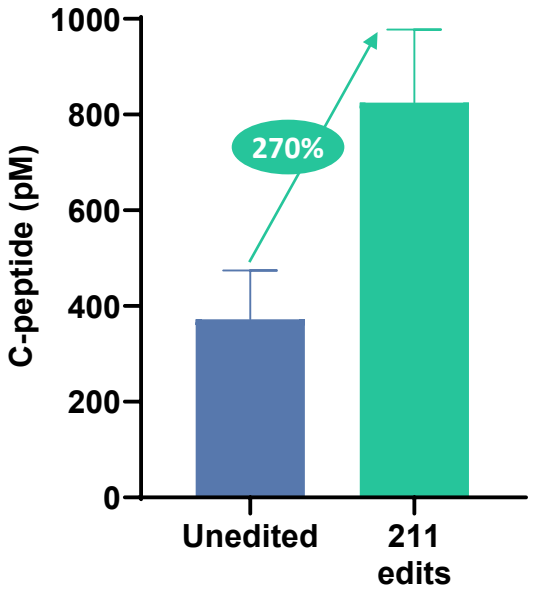
Adaptive & Innate – 211 cells survive in humanized mouse model



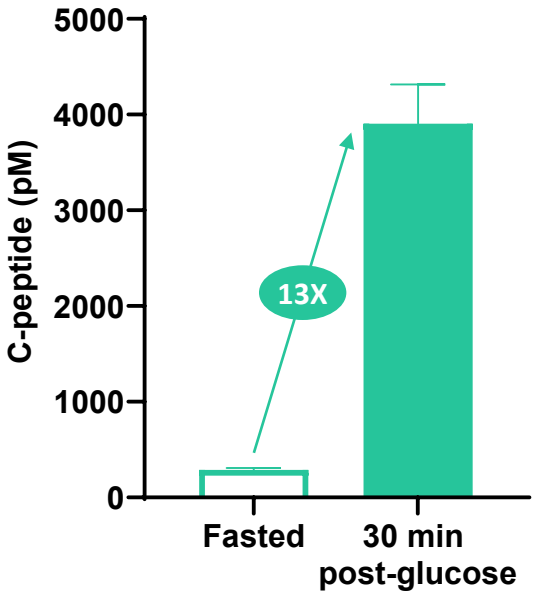
Demonstrates broad immune evasive potential of 211 cells – humanized mouse model contains human DC, B cells, T cells, NK cells, and monocytes

VCTX211 Edits Improve Stimuli-Responsive Insulin Production

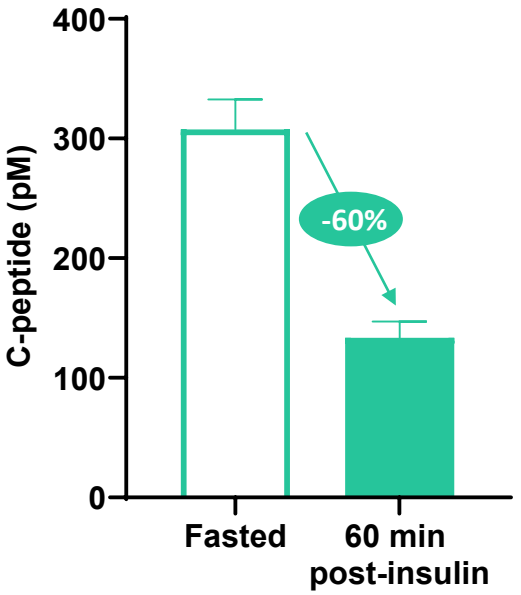
Increased insulin production



Robust glucose responsiveness



Preserved insulin sensitivity



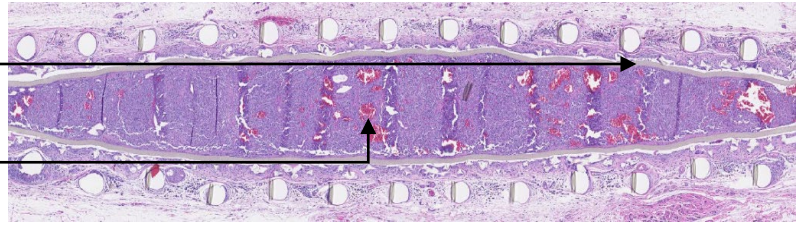
Assessed 12 weeks post-transplant

Robust Engraftment of VCTX211 in Nude Rat Model

Presence of cells demonstrates abundance of β-cells and avoidance of innate immune rejection

Device membrane

Blood vessels

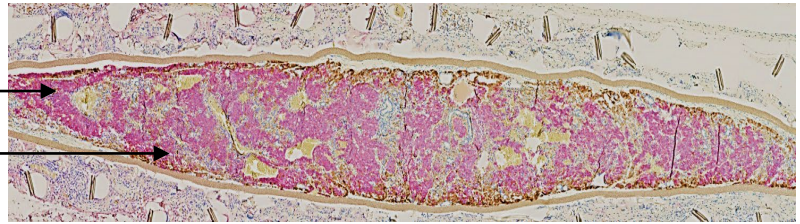


H&E section of VCTX211 in nude rats at 24 weeks show vascularization

Insulin/Glucagon

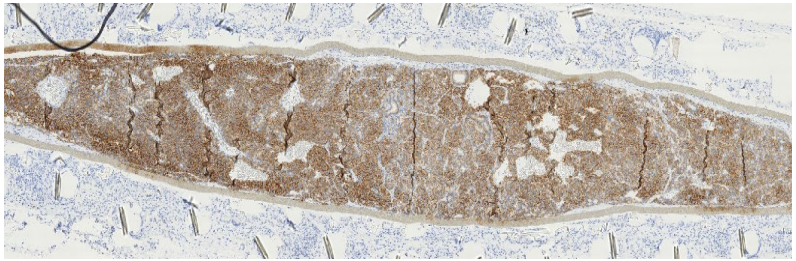
β

α



Cells shows favorable differentiation with a β/α ratio of approximately 2

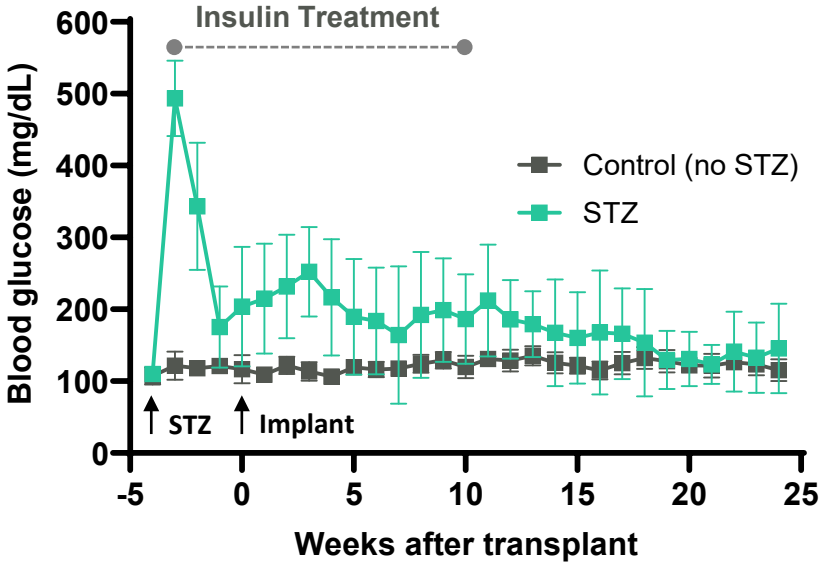
PD-L1



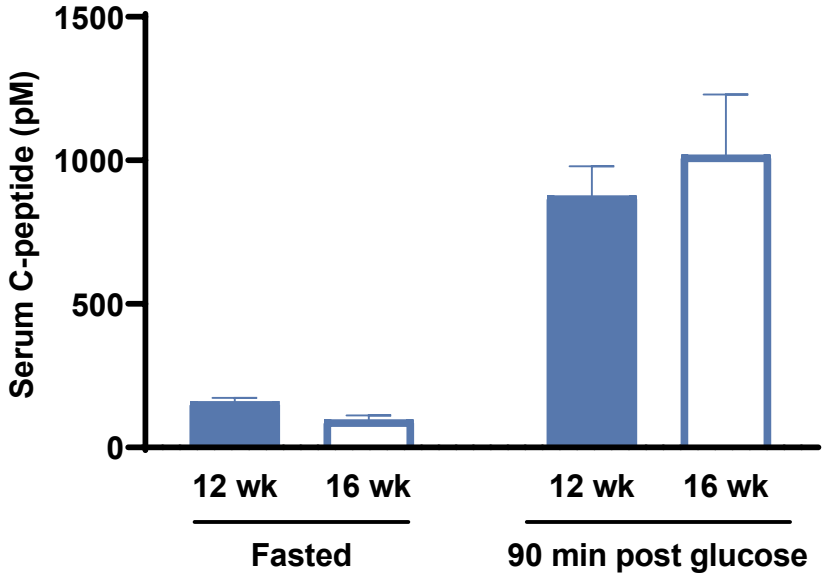
Retention of PD-L1 expression in long-term grafts

VCTX211 Reverses Hyperglycemia in Diabetic Rat Model

Normalization of blood glucose by 12-16 weeks



Treated rats maintain glucose sensitivity



Rats either treated with STZ ~4 weeks before VCTX211 implantation or untreated (normoglycemic control)

STZ: Streptozotocin (β-cell toxin)

Regenerative Medicine Pipeline

Program	Research	IND-Enabling	Clinical	Marketed	Status	Partner	Structure
VCTX210: Type I diabetes mellitus					Enrolling	VIACYTE®	Collaboration
VCTX211: Type I diabetes mellitus							
VCTX212: Type I/II diabetes mellitus							

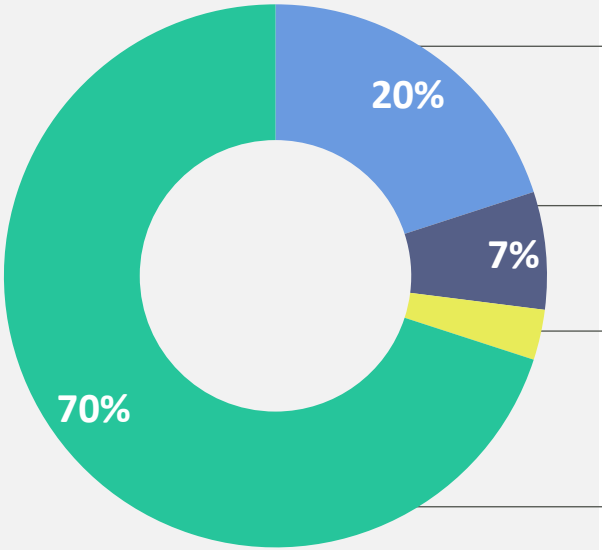
In Vivo Strategy

Jon Terrett, PhD, Head of Research

Our *In Vivo* Focus is on Disruption and Whole Gene Correction

Whole gene correction & gene disruption are needed to cover 90% of monogenic diseases

Editing approach required to address more than ~1/3 of the patient population with a single therapy for the 100 most prevalent severe monogenic diseases[1]



Gene disruption
Examples: TTR, HAE

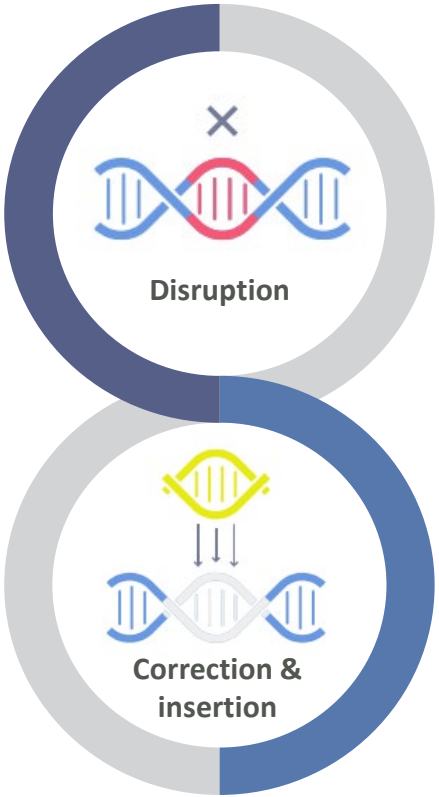
Single nucleotide correction
Example: A1AT

≤100 base pair correction
Example: Tyrosinemia type 1

Whole gene correction
Examples: Hemophilia

1. 100 most prevalent severe monogenic diseases addressable by somatic gene editing, excluding systemic diseases

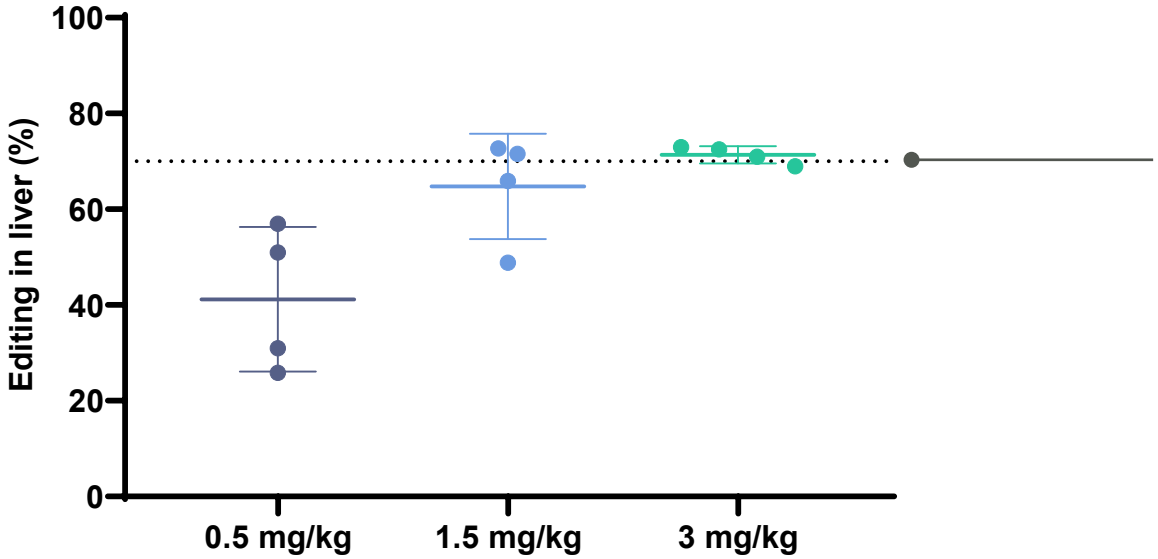
Becoming an *In Vivo* Leader – Our Strategy



- Establish a leading platform for *in vivo* gene disruption, starting in the liver
- Leverage our translational capabilities and balance sheet to advance a broad portfolio of disruption programs across both rare and common diseases
- Establish a leading whole gene correction platform, using AAV LNP and starting in the liver
- Advance whole gene correction to an HDR-independent, AAV-free methodology

Established a Leading mRNA/LNP Platform for Gene Disruption

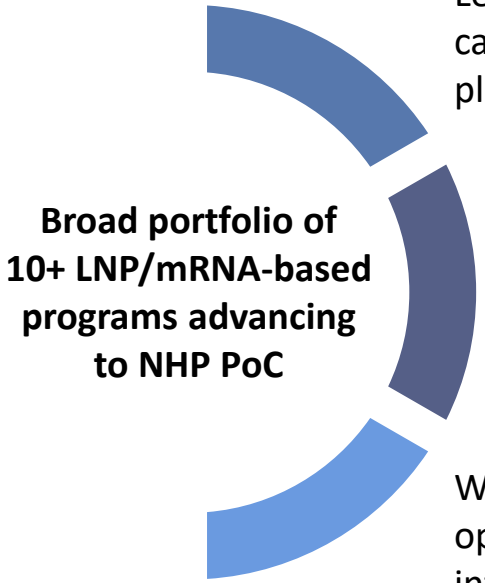
Dose-dependent liver editing up to 70% in NHPs



70+% editing in whole liver typically equates to 90+% hepatocyte editing and reduction in serum protein levels

Single intravenous dose of LNP formulated with Cas9 mRNA and gRNA

Advancing a Broad Portfolio of Gene Disruption Programs



Broad portfolio of 10+ LNP/mRNA-based programs advancing to NHP PoC

Leverage CRISPR's translational capabilities, balance sheet, and plug-and-play nature of LNP/mRNA

Advance multiple programs to NHP PoC stage, select programs proceed to clinical development

Wholly-owned *in vivo* portfolio creates opportunities for partnership as well as internal development

Cardiovascular

- ANGPTL3
- Lp(a)
- PCSK9
- Other undisclosed targets

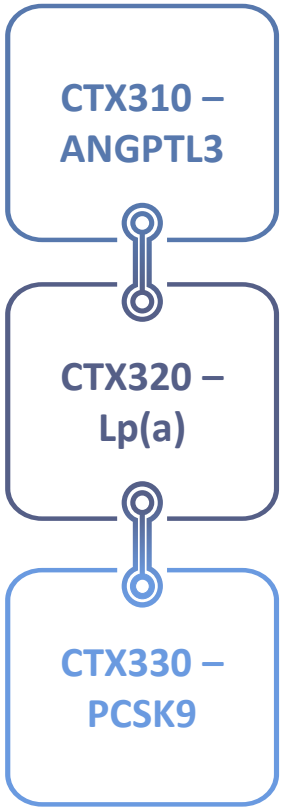
Other liver targets

- HAE
- TTR
- PH1
- Other undisclosed targets

Ocular

- Undisclosed targets

ASCVD Programs – Proven Benefit in a Once-and-Done Format

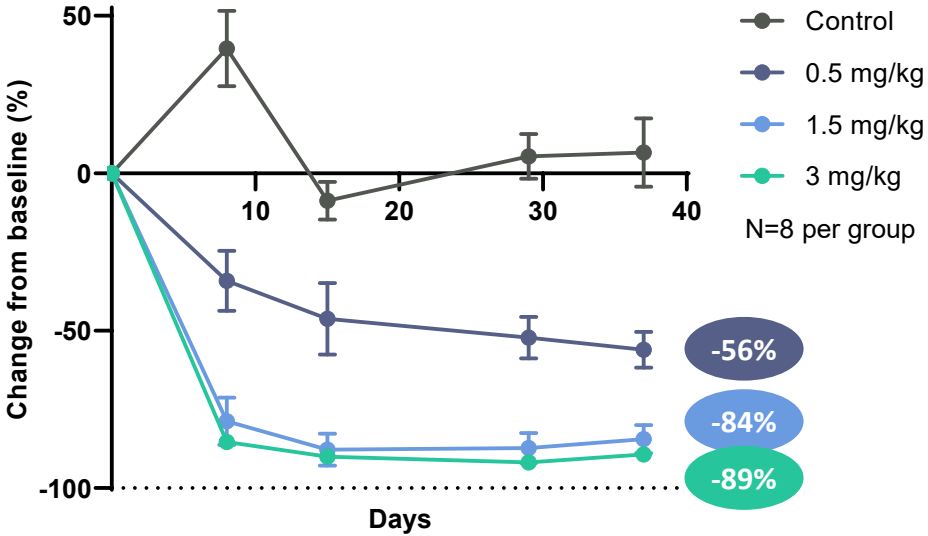


- Proven benefit based on natural human genetics (similar to BCL11A) and antibody / small RNA therapeutics
- Paradigm shift possible with single-dose, potentially lifetime durable editing approach
- Development paths starting with severe disease, and expanding to much larger patient populations
- Potential for combination therapy across the 3 targets

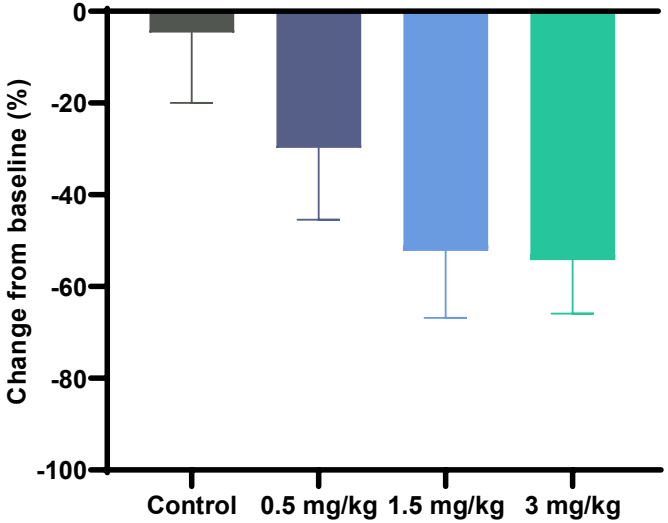
ASCVD: Atherosclerotic Cardiovascular Disease

CTX310: Potentially Transformative for Cardiovascular Disease

~90% reduction in serum ANGPTL3 protein in NHPs



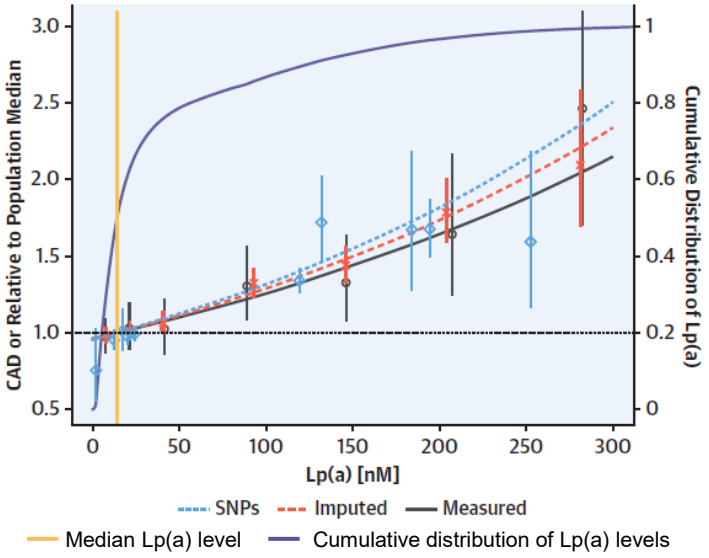
>50% reduction in serum triglycerides at one month



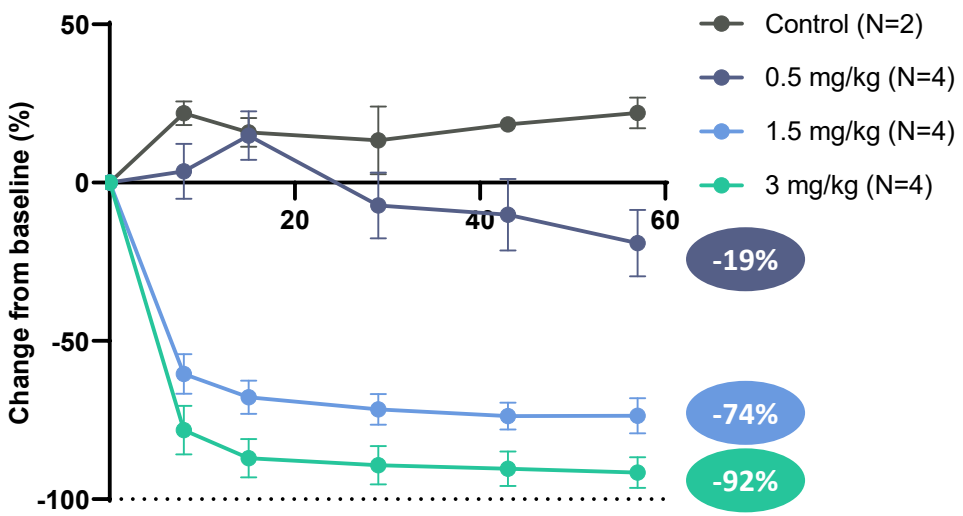
Progressing CTX310 program to the clinic in 2023

CTX320: Lp(a) is Emerging as an Ideal Target for ASCVD

Coronary artery disease risk increases with increasing Lp(a) level



>90% reduction in serum Lp(a) in NHPs

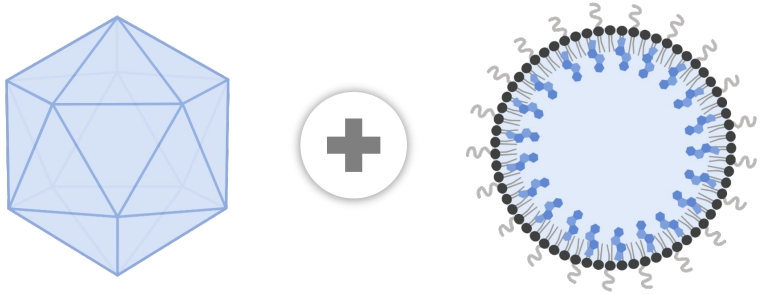


Progressing CTX320 program to the clinic after CTX310

Sources: Gudbjartsson, et al. *J Am Coll Cardiol*. 2019;74(24):2982–94.

Unlocking Whole Gene Correction and Insertion

AAV + LNP



- Proven technologies allow whole gene correction via repair mechanisms at specific loci
- Potential for improved consistency and durability compared to episomal gene transfer via AAV
- Ability to address majority of monogenic diseases, where mutations span the length of the gene

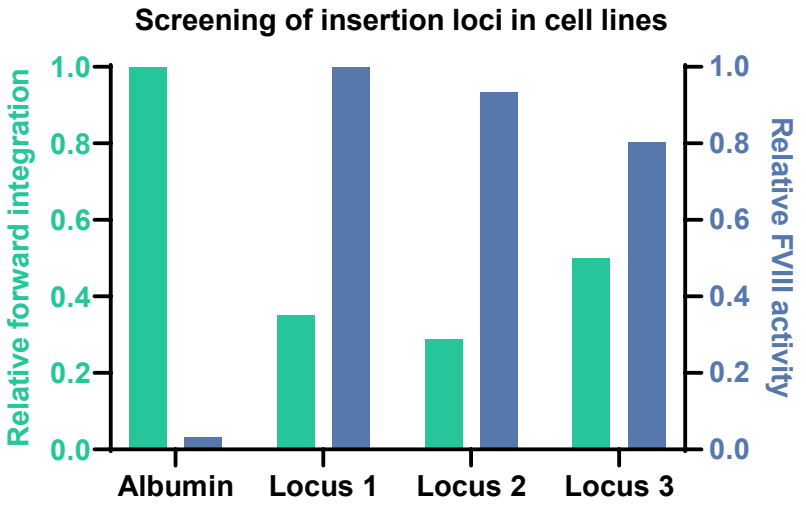
Next-generation technologies

CRISPRx

- Dedicated internal group focused on emerging technologies to allow HDR-independent and/or AAV-free whole gene correction/insertion
- Natural systems require further optimization of efficiency and specificity for clinical application
- Research ongoing focused on non-viral DNA delivery and all-RNA systems

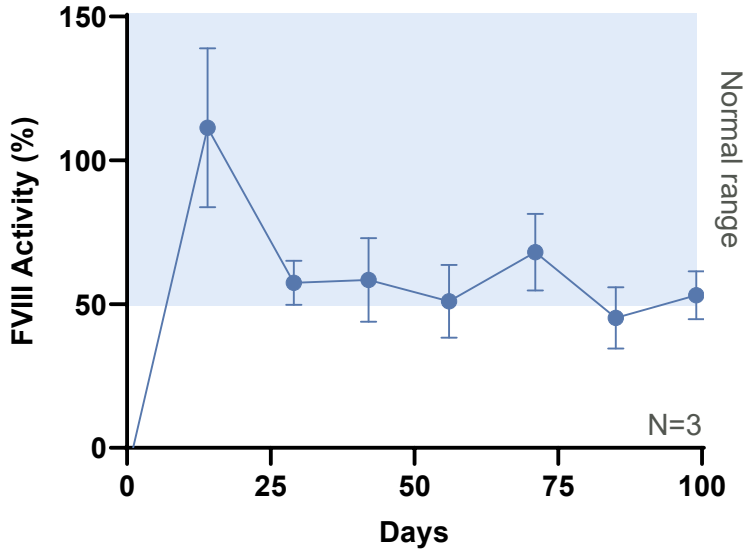
Whole Gene Insertion/Correction: Novel Safe Harbor Loci

Gene expression can be optimized by targeting different loci



Different transgenes require different insertion loci to achieve desired therapeutic effect

Normal levels of FVIII activity can be achieved in NHPs



LNP for CRISPR machinery + AAV for transgene

In Vivo Pipeline

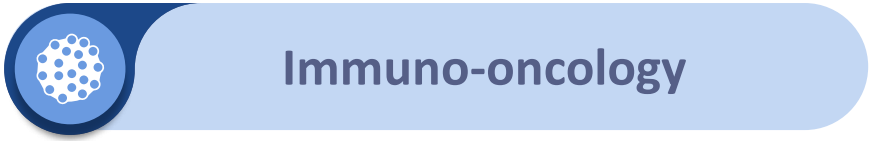
		Program	Research	IND-enabling	Clinical	Marketed	Partner	Structure
LNP	Disruption or deletion	CTX310: ANGPTL3						Wholly-owned
		CTX320: LP(a)						Wholly-owned
		CTX330: PCSK9						Wholly-owned
		Undisclosed CV programs						Wholly-owned
		Other gene disruption programs						Wholly-owned
		Undisclosed ocular program					BAYER	Collaboration
	Insertion	Hemophilia A						
		Undisclosed insertion program						Wholly-owned
AAV	Disruption or deletion	Friedreich's ataxia (FA)					CAPSIDA BIOTHERAPEUTICS	Collaboration
		Amyotrophic lateral sclerosis (ALS)						

VERTEX Partnered on several disease areas, including Duchenne muscular dystrophy (DMD), myotonic dystrophy type 1 (DM1), and cystic fibrosis (CF)

Closing

Advancing the Broadest Gene Editing Platform

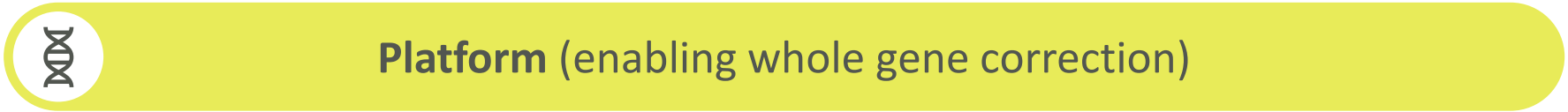
Targeted conditioning & *in vivo* editing to enable the next phase of exa-cel



Optimal edits & targets to unlock CAR-T in solid tumors

Multi-gen approach to unleash the combined power of editing & pluripotent stem cells

Proven translational capabilities plus robust LNP platform for rare & common diseases



Questions

CRISPR Therapeutics

www.crisprtx.com