



Creating transformative gene-based medicines for serious diseases

Bank of America Healthcare Conference
May 15, 2024

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CRISPR Therapeutics Today



Best-in-class technology, strategy, and execution culminating in historic approval of CASGEVY



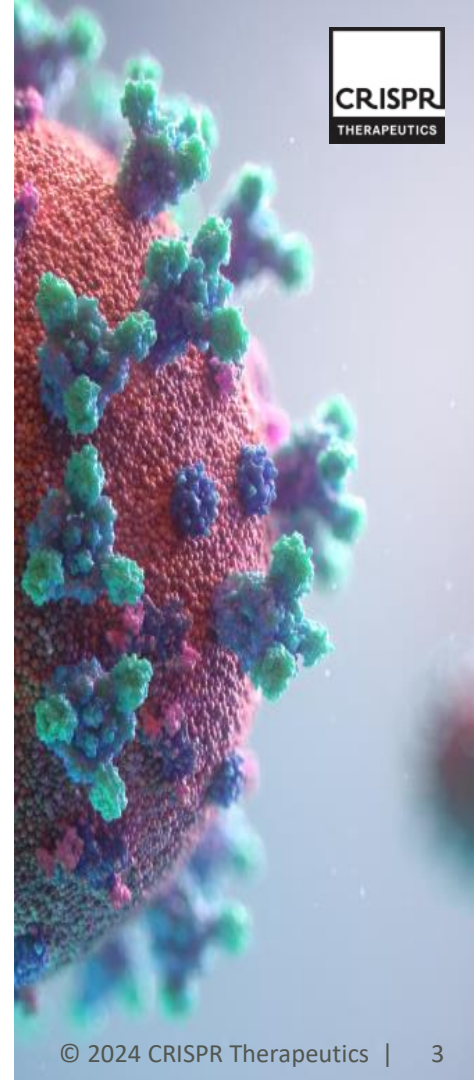
Three additional franchises with 5 programs in the clinic in oncology, autoimmune, cardiovascular, rare diseases, and diabetes



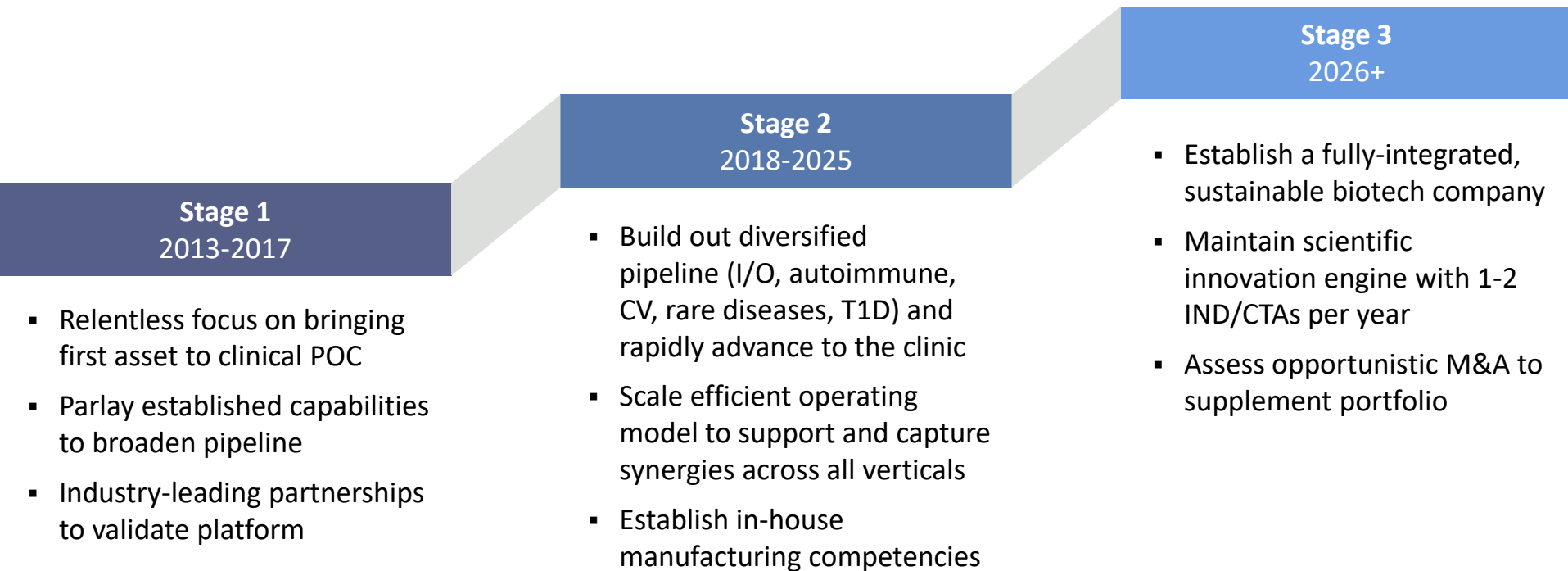
10 additional preclinical programs and continuous platform innovation across multiple next-generation technologies to enable new therapies



Disciplined operating model and capital efficiency



Advancing to the Next Phase of Growth



Sector-leading operating efficiency,¹ minimal dilution, and strong balance sheet

1. Based on analysis of trailing twelve-month operating expenses less non-cash items per clinical candidate

CASGEVY: Historic First Approval of a CRISPR-Based Medicine



Unparalleled speed and execution
to a landmark approval¹



WSJ

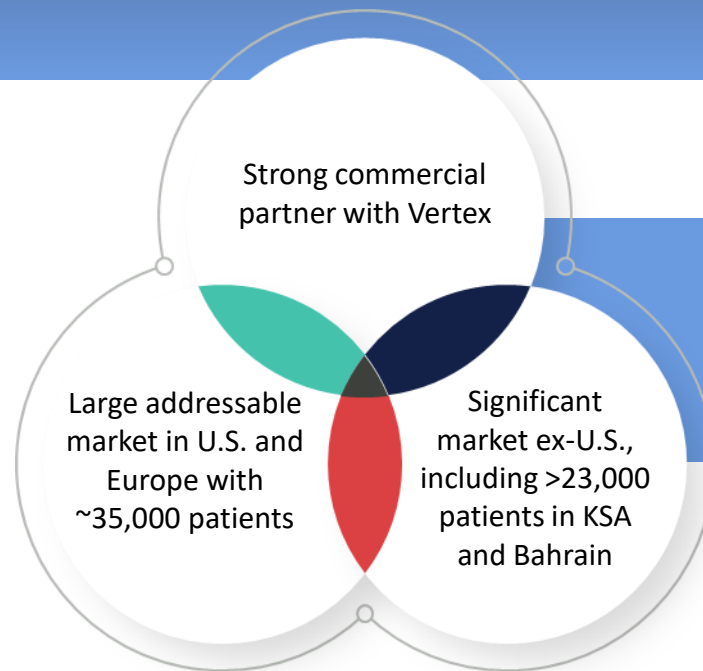
FDA Approves World's First Crispr Gene-Editing Drug for Sickle-Cell Disease

Landmark decision heralds a new type of medicine that
can tackle genetic conditions that are hard to treat



F.D.A. Approves Sickle Cell Treatments, Including One That Uses CRISPR

Well-positioned for commercial success



Foundational
Year in 2024

1. Approved by the U.S. FDA for the treatment of SCD in patients 12 years and older with recurrent vaso-occlusive crises (VOCs) and TDT in patients 12 years and older;. Granted conditional marketing authorization by the UK MHRA and Bahrain NHRA for patients 12 years of age and older with SCD with recurrent VOCs or TDT for whom hematopoietic stem cell transplantation is appropriate and a human leukocyte antigen matched related hematopoietic stem cell donor is not available. Also approved by the EMA and Saudi Food and Drug Agency for SCD and TDT.

Expanding the Addressable Patient Population

Near-Term: Targeted conditioning using Antibody-drug conjugate against c-Kit to expand addressable population for CASGEVY

Optimal Attributes



High on-target potency



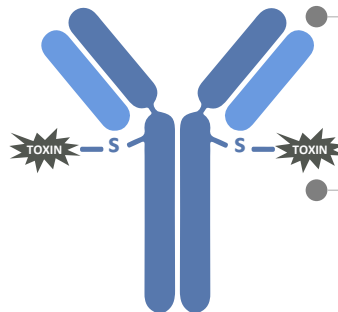
Low off-target & systemic toxicity



Rapid clearance from circulation



Established manufacturing



Proprietary **GMP monoclonal antibody** with **short half-life** targeting **c-Kit (CD117)**

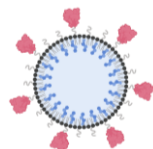
Validated **GMP toxin** with **HSC activity** and **reduced hydrophobicity** to limit non-specific toxicity

Long-Term: Targeted LNP and AAV based delivery systems to enable *in vivo* editing of HSCs¹

- Could enable a global cure for SCD and TDT and unlock the ability to address new indications
- Progressing multiple approaches that could solve this challenge
- Ongoing grant from the Bill & Melinda Gates Foundation



DELIVERY



Targeted LNP

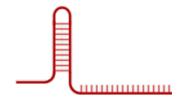


AAV

EDITING



mRNA
optimization



gRNA
modification

Three Additional Franchises Beyond CASGEVY

In Vivo **Common and Rare Diseases**

*Established
mRNA-LNP
platform for
liver editing*

Validated targets for CV, plus
additional programs in both
common and rare diseases

CAR T **I/O and Autoimmune**

*World's most
sophisticated CAR T
cell candidates,
manufactured
internally*

Multiple opportunities across
heme and solid cancers, plus
autoimmune indications

Type 1 Diabetes

*First-in-class edited
beta cell therapies
for T1D*

Multiple approaches for a beta cell
replacement product without long-
term immunosuppression

Platform
Next-generation editing and delivery

Advancing Plug-and-Play *In Vivo* Platform Across Multiple Diseases



Established plug-and-play LNP/
mRNA platform for *in vivo* gene
disruption, starting in the liver

~60-70% whole liver editing across
multiple targets, which translates to
near-complete editing in
hepatocytes^a

Potential to transform the treatment
paradigm for CV with
CTX310™, CTX320™, CTX330™
and CTX340™

First two programs in the clinic
with CTX310 targeting ANGPTL3
and CTX320 targeting Lp(a)

**CTX340 targeting AGT: Phase 1
planned trial initiation in 2H25**

Advancing *in vivo* programs in
additional rare diseases

One-time therapies that could recapitulate
the proven benefit of targets validated by
human genetics and other modalities

**CTX450 targeting ALAS1: Phase 1 trial
targeting initiation in 2H25**

Program	Indication(s)	Research	IND-enabling	Clinical
CTX310: ANGPTL3	Mixed dyslipidemias, HoFH ¹ , SHTG ² , and HeFH ³	●	●	●
CTX320: Lp(a)	ASCVD with elevated Lp(a)	●	●	●
CTX340: AGT	Refractory hypertension	●	●	●
CTX330: PCSK9	HeFH ³	●	●	●
CTX450: ALAS1	Acute hepatic porphyria	●	●	●

^aGao et al. 2008

¹ Homozygous familial hypercholesterolemia; ² Severe hypertriglyceridemia; ³ Heterozygous familial hypercholesterolemia

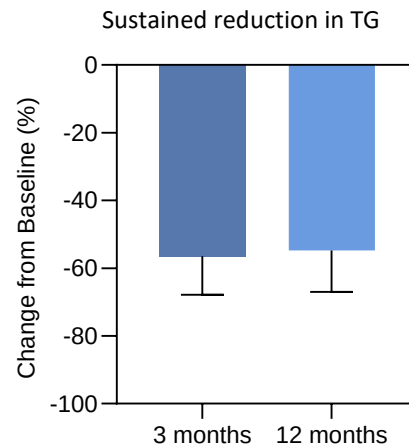
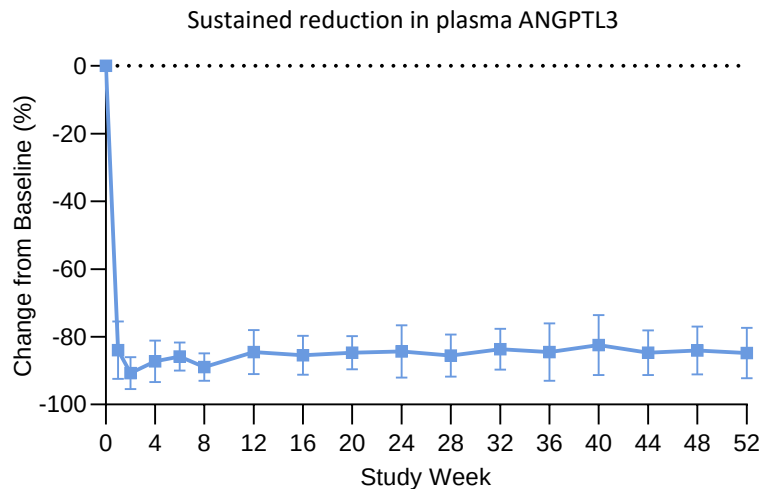
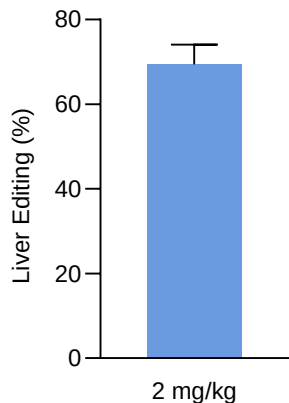
CTX310 Targeting ANGPTL3 for Cardiovascular Disease

Natural loss-of-function mutations in *ANGPTL3* are associated with reduced LDL-C, triglycerides (TG), and ASCVD risk without any negative impact on overall health^{1,2}

A one-time, CRISPR-based therapy could recapitulate the protective effect of naturally occurring loss-of-function variants in *ANGPTL3*

A single dose of CTX310 durably reduced ANGPTL3 and triglycerides in NHPs out to 1 year

~70% editing of *ANGPTL3*



CTX320 Targeting Lp(a), an Independent Risk Factor for ASCVD

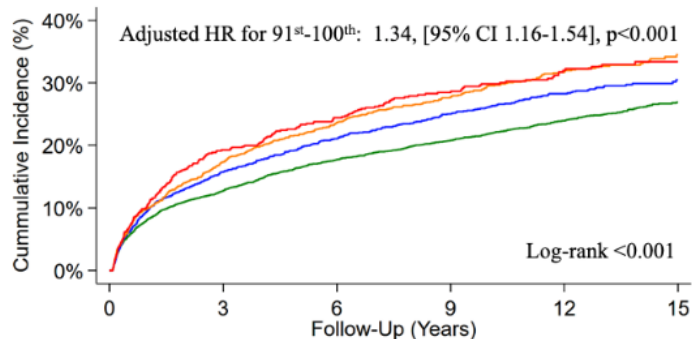
Elevated lipoprotein(a) [Lp(a)] levels increase ASCVD risk, as observed across numerous studies^{1,2,3,4,5}

Up to 20% of the global population has elevated Lp(a)^{6,7}, primarily determined by genetics⁸

A one-time, CRISPR-based therapy could recapitulate the protective effect of naturally low Lp(a)

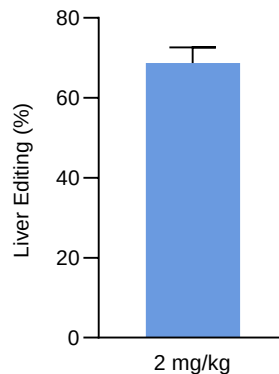
Lp(a) shows an independent association with MACE⁵

— **1st-50th percentile** 0-41 nmol/L
— **51st-70th percentile** 42-111 nmol/L
— **71st-90th percentile** 112-215 nmol/L
— **91st-100th percentile** >216 nmol/L

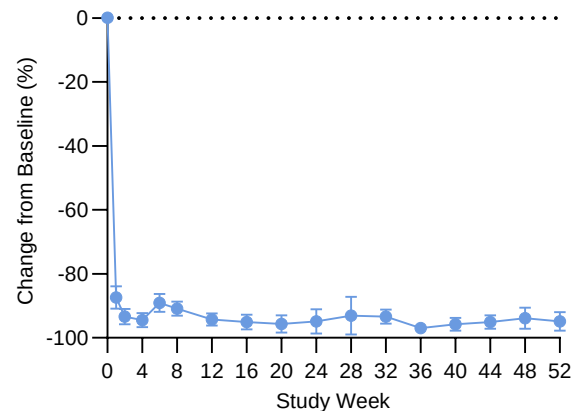


A single dose of CTX320 durably reduced Lp(a) in NHPs out to 1 year

~70% editing of LPA



~95% reduction in plasma Lp(a)



Note: Single dose of CTX320 (2 mg/kg) administered to non-human primates (NHPs) (N=4) on Day 1; study ongoing
1. Enas et al. 2019; 2. Gurdasani et al. 2012; 3. Laschkolnig et al. 2014; 4. Emdin et al. 2016; 5. Berman et al. 2023;
6. Nordestgaard et al. 2010; 7. Varvel et al. 2016; 8. Langsted et al. 2021

Presented at the American Heart Association Scientific Sessions. 11 Nov 2023

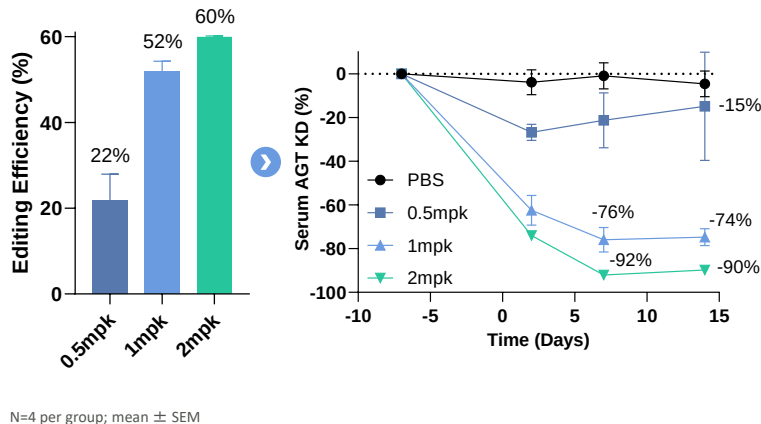
CTX340 Targeting AGT For Refractory Hypertension

Hypertension is the leading cause of cardiovascular morbidity and mortality worldwide^{1,2}

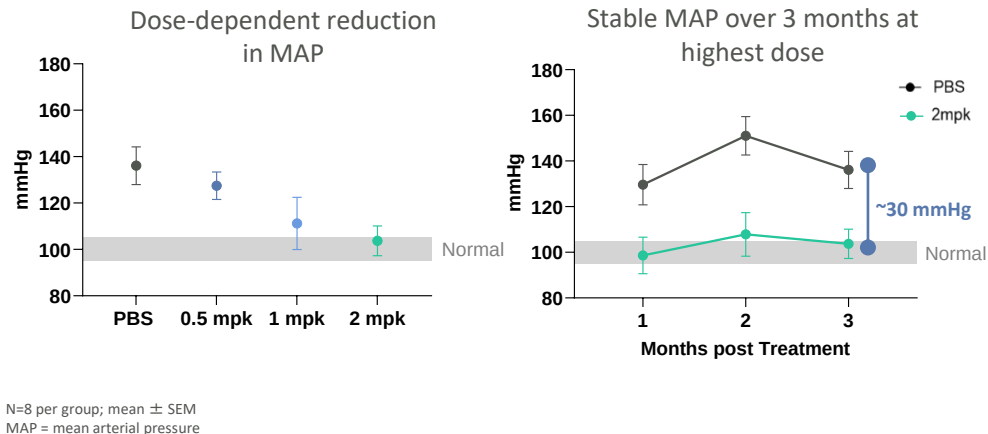
Refractory hypertension defined as uncontrolled blood pressure despite use of ≥ 5 or more antihypertensives at maximal tolerated doses³

A one-time, CRISPR-based therapy targeting angiotensinogen (AGT) could durably lower blood pressure

Up to 60% editing and 90% serum AGT in SHR^a model



A single dose of CTX340 led to dose-dependent, durable reduction in blood pressure



1. Zhou et al. 2021; 2. Danaei et al. 2009; 3. Acelajado et al. 2019; 4. Jones et al. 2020

a. SHR: spontaneous hypertensive rat

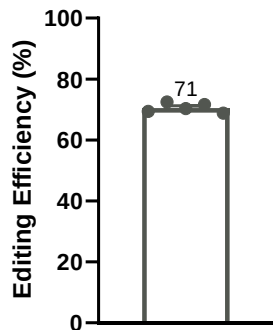
CTX450 Targeting ALAS1 for AHP

Acute hepatic porphyrias (AHP) are inherited metabolic disorders caused by deficiencies of specific enzymes in the heme biosynthetic pathway.^{1,2} The rate-limiting enzyme of the heme biosynthetic pathway is hepatic 5-aminolevulinic acid synthase (ALAS1)^{3,4,5}

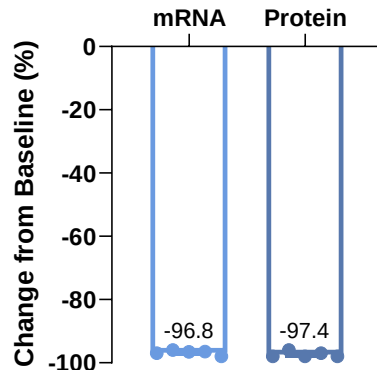
A one-time, CRISPR-based therapy could durably reduce disease-associated biomarkers, potentially leading to an amelioration of AHP attacks

A single dose of CTX450 showed deep reductions in ALAS1 mRNA and protein leading to normalization of ALA/PBG in a disease model

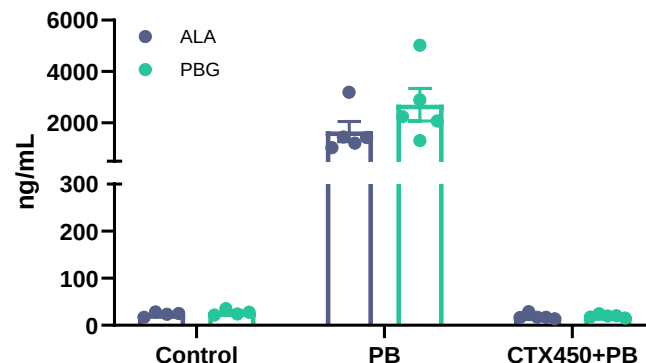
~70% editing of ALAS1



~97% mean mRNA and protein reduction



Leading to reduction of ALA^a and PBG^b biomarkers in PB^c challenge model



N=5 per group; mean $\pm$ SEM

1. Anderson et al. 2001; 2. Chan et al. 2015; 3. Granick S. 1963; 4. deMatteis 1967; 5. Handschin et al. 2005

a. 5-aminolevulinic acid (ALA), b. porphobilinogen (PBG), c. phenobarbital (PB)

Our Gene-Edited Allogeneic CAR T Franchise



Advancing the most sophisticated CAR T cell candidates in the clinic against multiple opportunities across heme and solid cancers, plus autoimmune indications

First-generation: CTX110 and CTX130

Proof-of-concept that **allogeneic CAR T cells can produce durable remissions** following a standard lymphodepletion regimen

Next-generation: CTX112 and CTX131

Preliminary clinical data suggest **next-generation programs may improve upon the clinical profile of the first-generation**

Additional indications and targets

Advancing in new areas, e.g., autoimmune disease and autologous CAR T in solid tumors

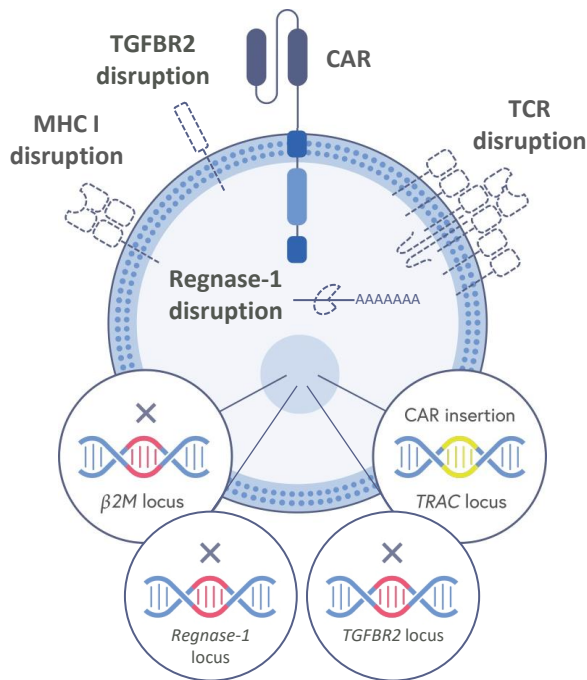
Program	Indication(s)	Research	IND-enabling	Clinical	Partner
CTX112 Anti-CD19 allogeneic CAR T	B cell malignancies	●	●	●	
	Systemic lupus erythematosus (SLE)	●	●	●	
CTX131 Anti-CD70 allogeneic CAR T	Renal cell carcinoma and other solid tumors	●	●	●	
	Hematological cancers	●	●	●	
Anti-GPC3 Autologous CAR T	Hepatocellular carcinoma	●	●	●	
Anti-CD70 Allogeneic CAR-NK	Solid and hematological cancers	●	●	●	

CTX112™ and CTX131™ Incorporate Novel Potency Edits

Next-generation CRISPR gene-edited allogeneic CAR T chassis

Novel Potency Edits

- **Regnase-1 KO:** Increase functional persistence, cytokine secretion and sensitivity, and effector function
- **TGFBR2 KO:** Reduce tumor microenvironment inhibition of multiple CAR T cell functions



- **TCR KO:** Prevent GvHD
- **CAR KI:** Site-specific insertion into TRAC locus without using lentivirus
- **MHC I KO:** Improve persistence in the allogeneic setting and avoid need for more toxic lymphodepletion

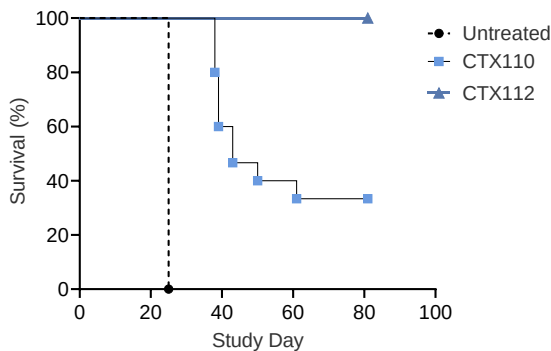
CTX112 and CTX131 utilize the same CRISPR-edited allogeneic T cell chassis, but CTX112 incorporates a CD19-targeted CAR while CTX131 incorporates a CD70-targeted CAR and knock-out of CD70

CTX112 and CTX131 Build Upon First Gen CAR T's in Oncology

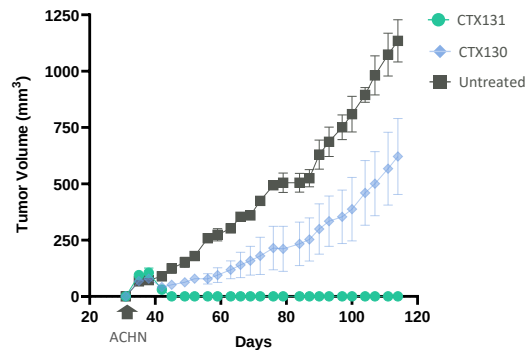
First-generation CAR Ts, CTX110 & CTX130

Proof-of-concept that our allogeneic CAR T cells can produce durable remissions following a standard LD regimen in hematological malignancies as well as solid tumors

Potency edits in CTX112 lead to extended survival in Nalm6-Luc mice compared to CTX110



CTX131 eliminates different xenograft tumor models upon rechallenge without exhaustion

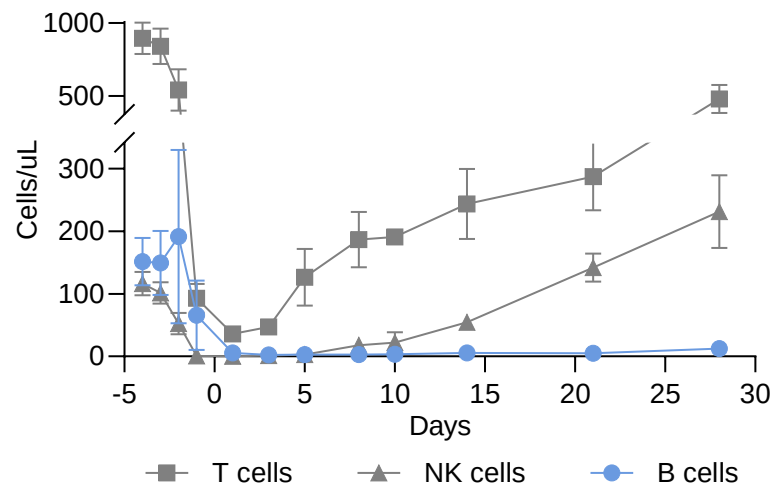


Preliminary clinical data in next generation CAR T suggests improvement on first generation clinical profile, including significantly higher CAR T cell expansion & functional persistence

CTX112: Significant Opportunity in Autoimmune Diseases

- **Allogeneic CAR T cells produce deep B cell depletion** in B cell malignancies, as observed with CTX110
- **CD19-directed autologous CAR T cells have produced durable remissions in multiple autoimmune indications** in early clinical studies (e.g., Mueller et al. ASH 2023)
- **CTX112 has the potential to provide similar results with several potential advantages:**
 - Increased scalability
 - Dramatically decreased COGS
 - Reduced risk of CRS, ICANS, and prolonged B cell aplasia
 - Improved patient experience with no need for apheresis

B cell depletion following CTX110 infusion among patients with detectable B cells at baseline (N=9)



Median time to B cell recovery: 178 days (range: 44-465)

On track to initiate trial in 1H 2024 starting in systemic lupus erythematosus (SLE)
with expansion opportunities in additional autoimmune indications

CTX112 is Differentiated from Other CD19 Therapies

CTX112		Autologous CD19 CAR Ts	Other Allogeneic T or NK cells	T-cell engagers	mAbs or ADCs
Safety		✓ Site specific CAR insertion		✓ Reduced risk of accumulated AEs with chronic dosing	✓
Efficacy			✓ More potency w/ next-generation edits	✓ Deeper depletion of B-cells Ability to reach tissue resident B-cells	✓
Patient experience		✓ No apheresis		✓ Single course of treatment	✓
Feasibility		✓ Faster trial & lower COGS	✓ Commercial ready GMP mfg		

CTX112 is well positioned to be a leading treatment option for systemic lupus erythematosus (SLE)
with expansion opportunities into additional autoimmune indications

Three Parallel Efforts in Type 1 Diabetes (T1D)

Gene-editing is key to achieving the goal of developing a beta-cell replacement product to treat diabetes without requiring long-term immunosuppression

1

CTX211

First-in-class edited beta-cell replacement therapy:

Encapsulated pancreatic progenitor cells derived from pluripotent stem cells with gene-edits for immune evasion and cell survival

Phase 1 clinical trial ongoing

2

Deviceless approach

Unencapsulated pancreatic progenitor cells derived from edited pluripotent stem cells

Advancing through research phases

3

Non-exclusive license with Vertex

Covers Vertex's gene-edited hypoimmune programs for T1D

\$170M in upfront and milestone payments to CRISPR in 2023

Up to \$160M in additional research and development milestones, plus royalties on future products

Wholly owned, with ability to leverage
ViaCyte cell lines and IP

In-House Manufacturing Expertise Gives Us Flexibility



Manufacturing CTX112 and CTX131 at our internal GMP facility



These candidates exhibit increased manufacturing robustness, with a higher and more consistent number of CAR T cells produced per batch



Potential for significantly lower COGS and greater scalability



Capacity and flexibility to manufacture additional programs and modalities (e.g., mRNA, iPSC)



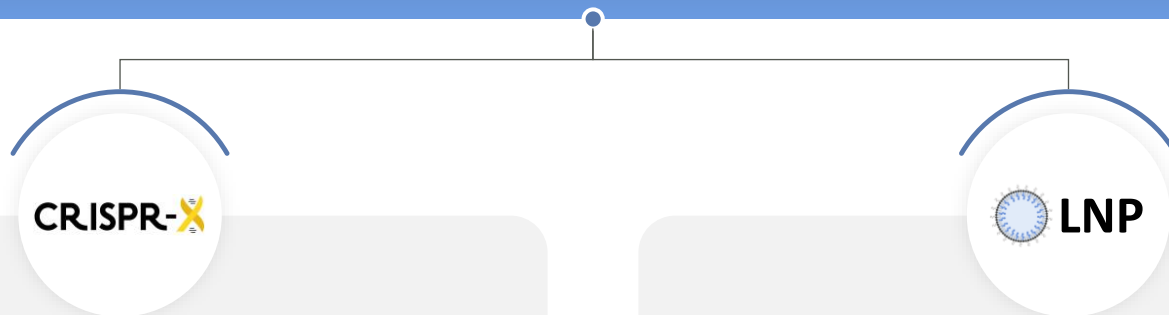
Next-Generation Editing: Poised to Continue Our Leading Role



The race to bring next-generation gene-editing technologies to the clinic has just begun

Both editing and delivery expertise needed to make the required edit in the required location

No one editing approach will dominate – each disease will have its own optimal approach



Dedicated internal research group focused on emerging technologies for gene correction and insertion, including non-viral DNA delivery and all-RNA systems

Dedicated LNP group supporting liver-directed and extrahepatic *in vivo* programs with novel lipids and formulations, targeting moieties, etc.

Most next-generation editing technologies combine the RNA-guided endonuclease activity of Cas9 with a fused effector domain, e.g., a reverse transcriptase – **we have issued foundational IP covering such fusions**

Broad and Diversified Pipeline



	Program	Disease	Research	IND-enabling	Clinical	Approved	Partner	Structure
Heme	CASGEVY ¹	Severe sickle cell disease (SCD)						Collaboration
		Transfusion-dependent β -thalassemia (TDT)						
	Next-generation conditioning	Various						Wholly owned ²
	In vivo editing of HSCs	Various						Wholly owned ²
CAR-T I/O & Autoimmune	CTX112	B cell malignancies						Wholly owned
	Anti-CD19 allogeneic CAR T	Systemic lupus erythematosus (SLE)						
	CTX131	Renal cell carcinoma and other solid tumors						Wholly owned
	Anti-CD70 allogeneic CAR T	Hematological cancers						
	Other CAR T (GPC3) & CAR NK	Various						Collaboration
In Vivo Cardiovascular & Rare Disease	CTX310: ANGPTL3	Mixed dyslipidemias, HoFH ⁴ , SHTG ⁵ , and HeFH ⁶						Wholly owned
	CTX320: Lp(a)	ASCVD with elevated Lp(a)						Wholly owned
	CTX340: AGT	Refractory hypertension						Wholly owned
	CTX330: PCSK9	HeFH ⁶						Wholly owned
	CTX450: ALAS1	Acute hepatic porphyria (AHP)						Wholly owned
T1D	CTX211	Type I diabetes mellitus						Wholly owned
	Deviceless approach	Type I diabetes mellitus						Wholly owned
Other disclosed partnered	Duchenne's muscular dystrophy (DMD)							License
	Myotonic dystrophy type I (DM1)							Collaboration
	Type 1 diabetes mellitus (T1D)							License
	Cystic fibrosis (CF)							License

1. Currently approved in some countries for certain eligible patients with SCD or TDT; 2. Collaboration with Vertex for applications in β -thalassemia and SCD; 3. CRISPR retains commercial rights; (4) Homozygous familial hypercholesterolemia; (5) Severe hypertriglyceridemia; (6) Heterozygous familial hypercholesterolemia

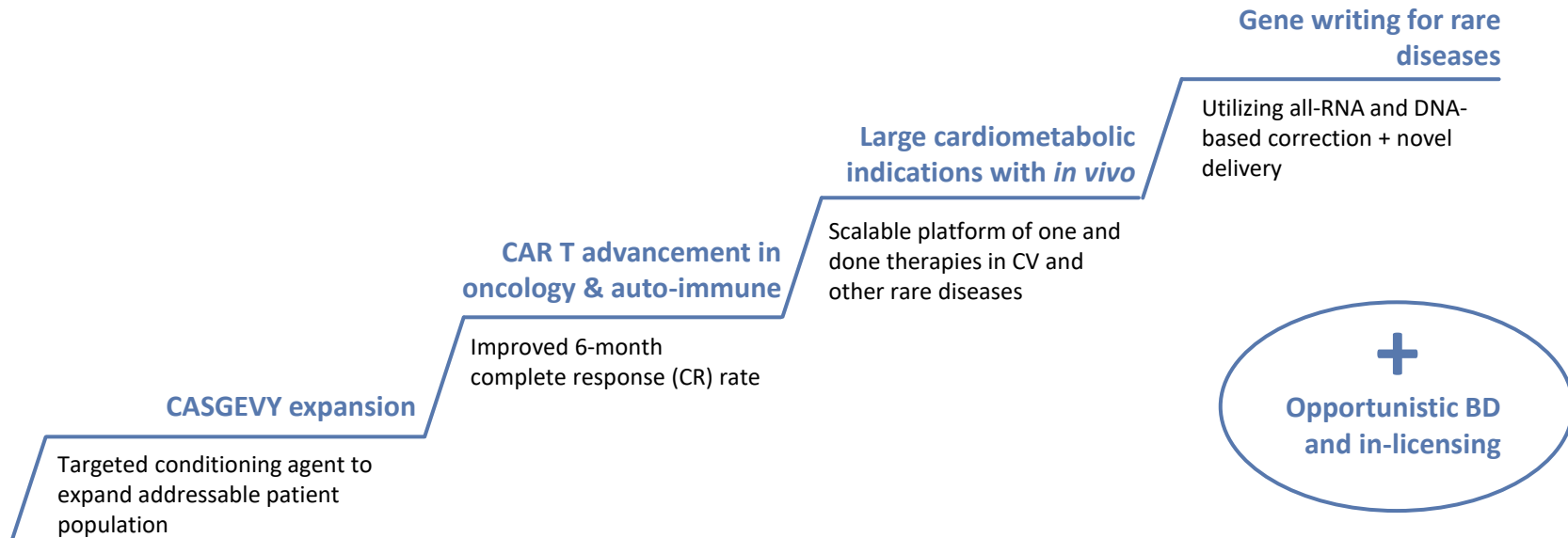
Several Upcoming Catalysts Across Portfolio



	Program	Disease	Status
Heme	CASGEVY	SCD and TDT	Launch ongoing – 2024 is a foundational year
I/O & Autoimmune	CTX112 - allo CD19 CAR-T	B-cell malignancies	Trial ongoing – data update in 2024
		SLE	Trial on track to be initiated 1H 2024
	CTX131 - allo CD70 CAR-T	Solid tumors	Trial in RCC ongoing – accruing data from early cohorts
		Heme malignancies	Trial on track to be initiated 1H 2024
In Vivo	CTX310 - ANGPTL3	Dyslipidemias	Trial initiated – targeting completion of dose escalation in 2024
	CTX320 - Lp(a)	ASCVD with elevated Lp(a)	Trial initiated – targeting completion of dose escalation in 2024
	CTX340 - AGT	Refractory Hypertension	Trial targeting initiation in 2H 2025
	CTX450 - ALAS1	Acute Hepatic Porphyria	Trial targeting initiation in 2H 2025
T1D	CTX211 – gene-edited beta cell replacement	Type 1 diabetes	Trial ongoing

How Do We Go From Sector Leader to Industry Leader?

Multiple levers to create value; opportunity to be fully integrated, sustainable biotech by 2028



CASGEVY approval, launch execution and geographic expansion in severe SCD and TDT¹

Key investments in people, technology, and manufacturing capabilities/scalability

Strong balance sheet² to support value drivers with ROIC focus



CRISPR Therapeutics

www.crisprtx.com