Guide identification for CRISPR-Cas9 engineering of allogeneic T cell therapies

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Caribou Biosciences company snapshot

Leading CRISPR genome editing company

- Caribou was founded in 2011 by CRISPR pioneers including Jennifer Doudna and Martin Jinek
- Foundational computational infrastructure and cell engineering expertise

Best-in-class, next-generation CRISPR technology

- Higher specificity than first generation CRISPR-Cas9
- Strong IP portfolio

Caribou is advancing a therapeutic product pipeline

- *ex vivo*, gene-edited cell therapies for immuno-oncology
- Bugs as drugs – engineered gut microbes to produce therapeutic metabolites, alter drug efficacy, or otherwise impart disease-modifying impact

Potential areas for partnering

- Lead Caribou program(s)
- Target-by-target, product-by-product collaboration in I/O, other cell therapies, gene therapies

Company snapshot

$41.5M financing to date

Investors include F-Prime Capital, Novartis, Maverick

Own equity of Intellia Therapeutics (NASDAQ: NTLA)

~60 employees

~25 issued US patents

Caribou therapeutic pipeline

- *ex vivo* immune cell therapy
  - –Caribou is using next-generation chRDNA platform to advance allogeneic CAR-T cell therapies
- Bugs as drugs
  - –Caribou has built a dedicated team of microbial engineers to develop technology POC toward therapeutic applications

Program	Cell type	Target	Edit type	Discovery	IND-enabling
CB-010	T cell	CD19	CAR into TRAC, PDCD1 KO		
CB-011	T cell	Undisclosed	Multiplex: 2 knock-ins		
CB-020	Immune cell	Undisclosed	Undisclosed		
CB-031	Gut microbe	Undisclosed	Undisclosed		

Caribou has retained commercial rights to all programs

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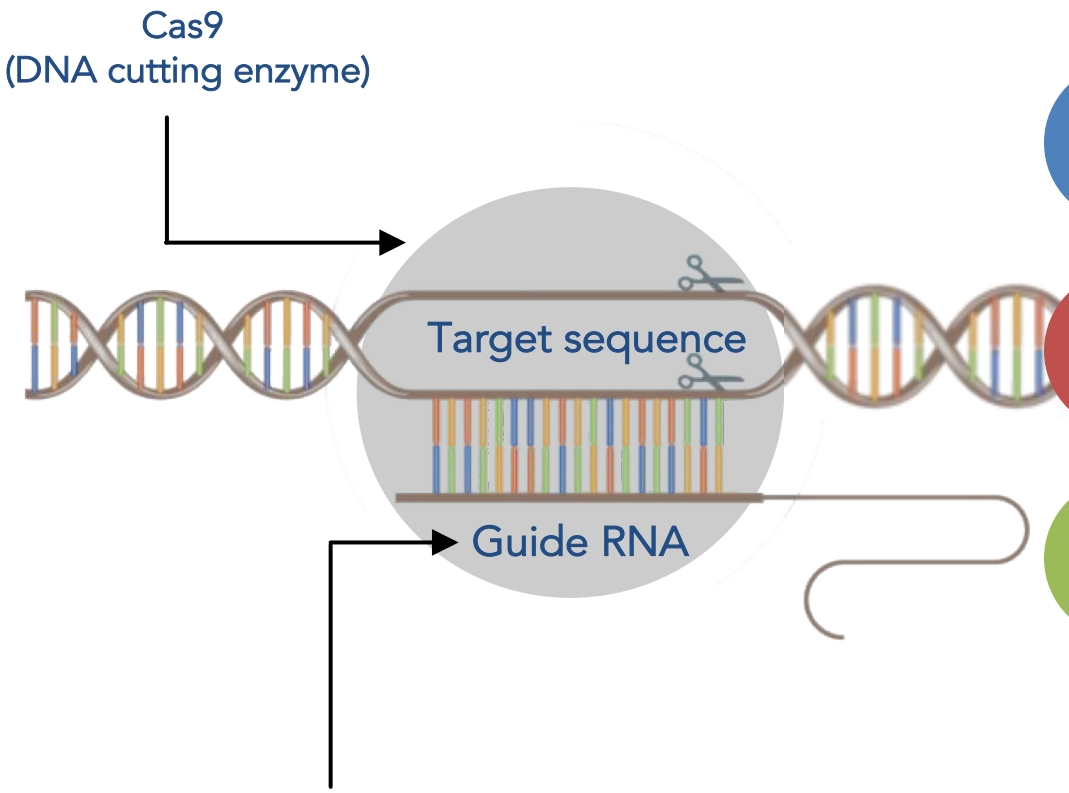
CRISPR editing enables target-specific changes in a variety of cell types



Engineering of guide RNA is the basis for next-generation genome editing technology

Cas9 generates site-specific double-strand break in target DNA

Cut repaired via NHEJ

Cut repaired with donor via HDR

Deletion of target gene

Insertion of new sequence

T cell

NK cell

Cell of choice

iPSC

Microbe

Cell-based medicines

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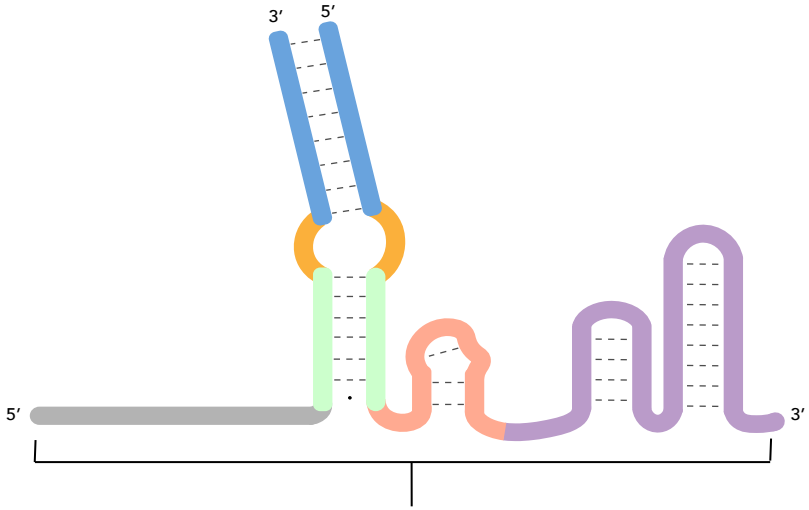
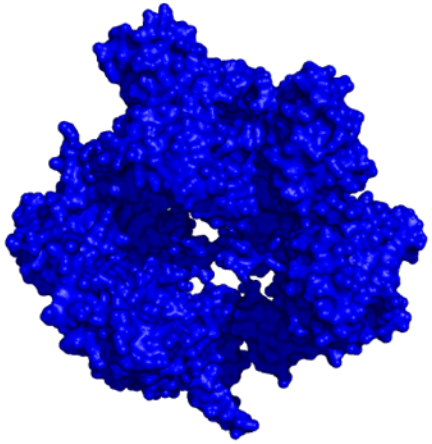
Next generation CRISPR guides for precision gene editing

CRISPR hybrid RNA-DNA (chRDNAs)



DNA nucleotides at multiple sites in the guide

+

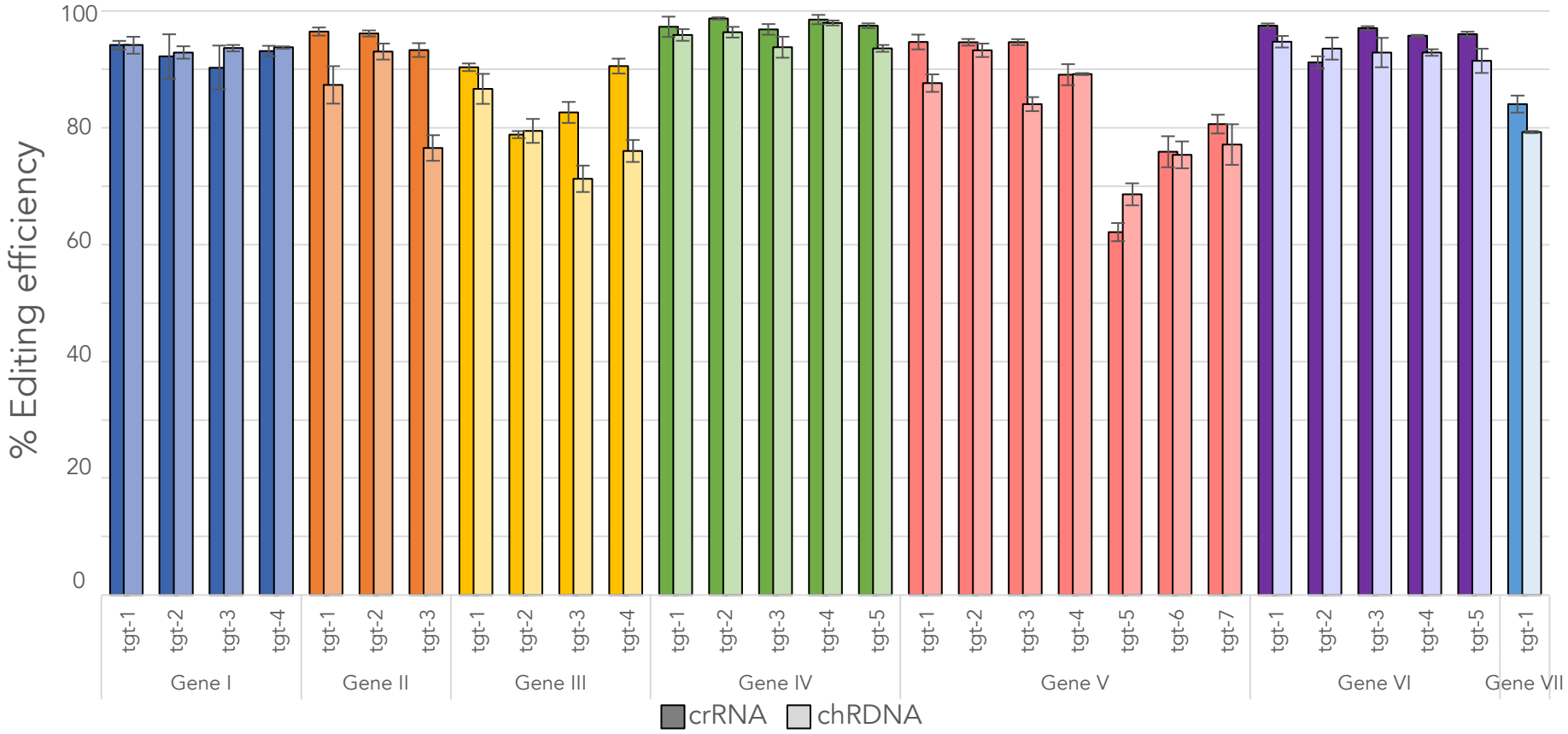


Cas9

While retaining high on-target editing efficiency, chRDNAs significantly reduce off-target editing relative to first-gen CRISPR in human primary cells

- **Caribou has an exclusive license in a broad field of therapeutics**
- **3 issued U.S. patents related to Cas9 chRDNAs**
- **Patent expiration dates in 2036+**

chRDNAs can be designed to efficiently edit a variety of genes



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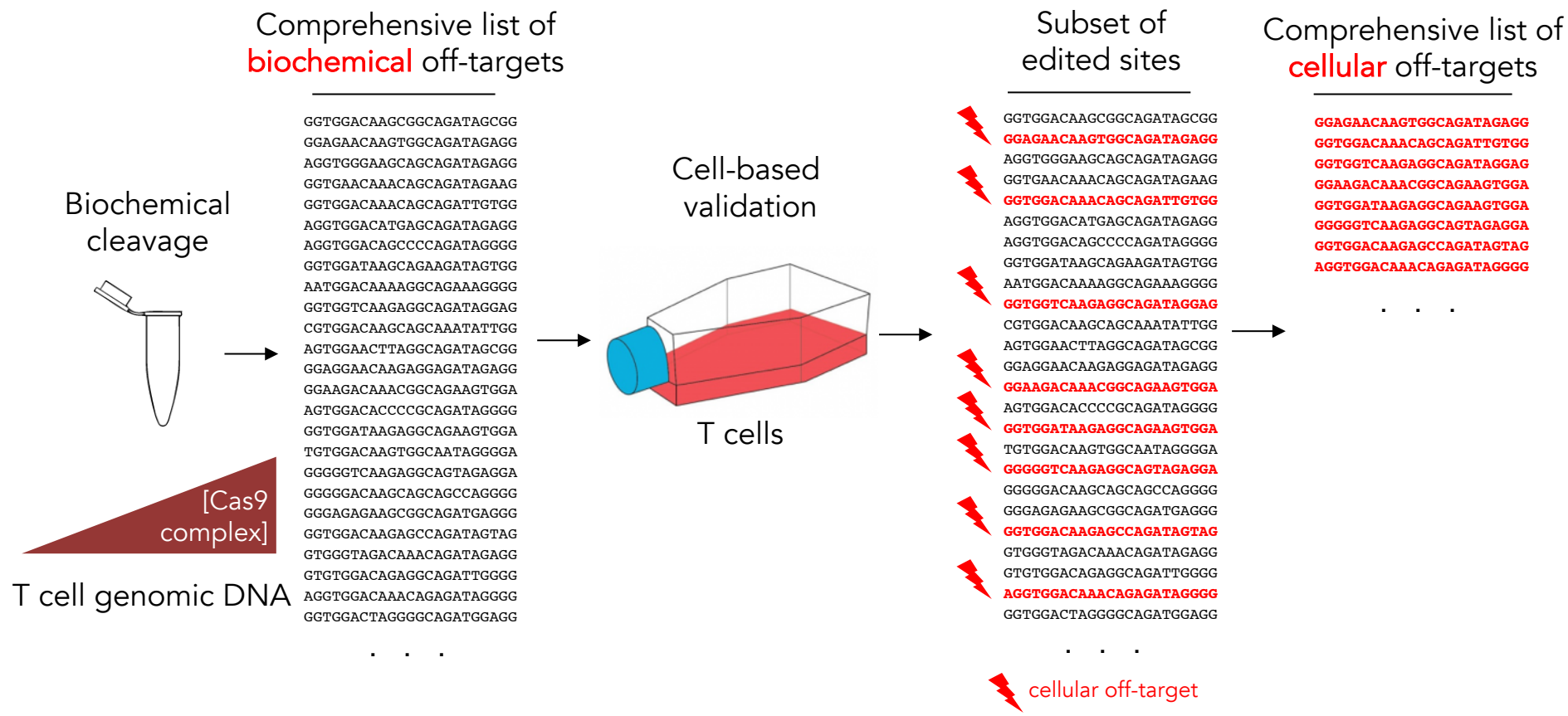
Off-target analysis and validation using the SITE-Seq® assay



Cameron et al, Mapping the genomic landscape of CRISPR-Cas9 cleavage, Nature Methods, 2017

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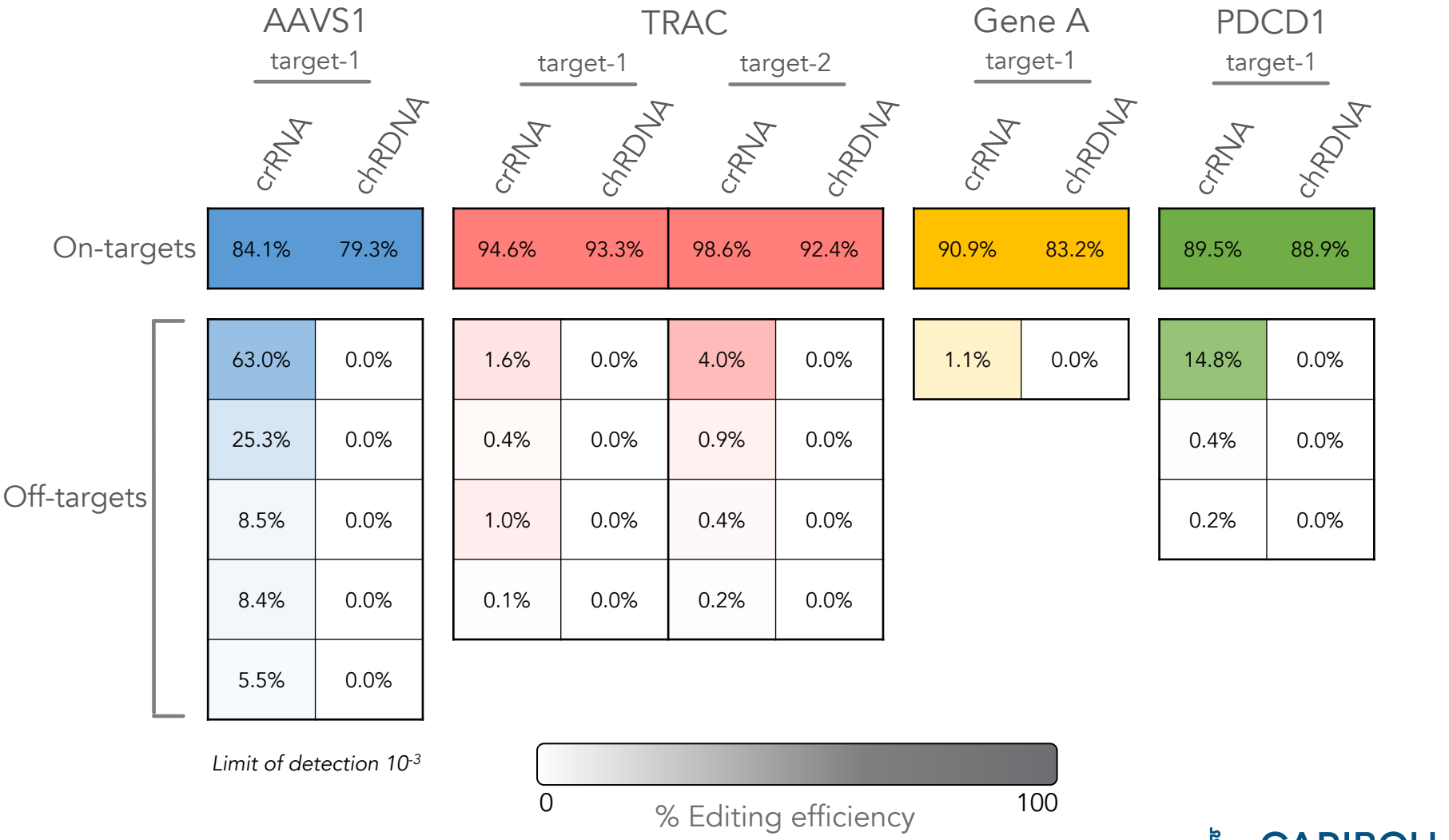
chRDNAs consistently improve specificity across multiple targets



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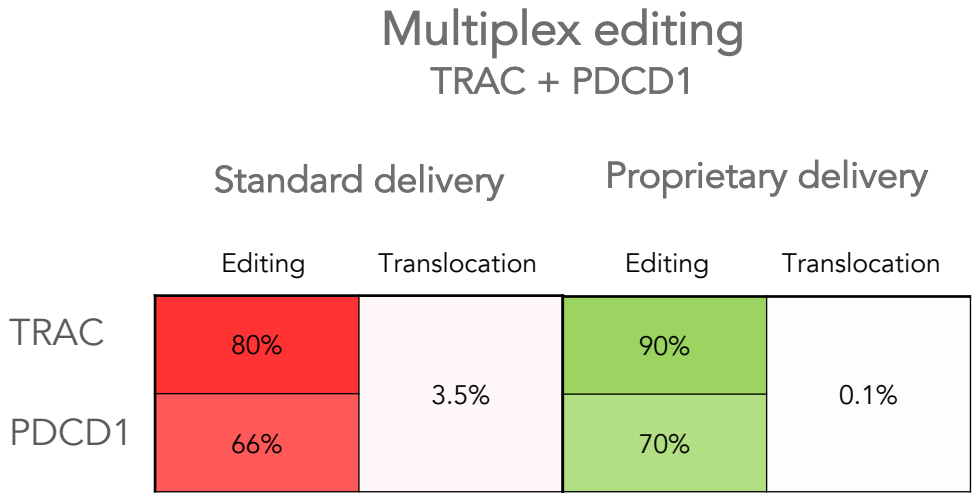
chRDNAs enable high efficiency multiplex editing with reduced translocations



Proprietary delivery approach for chRDNAs results in robust editing efficiency and significantly decreases translocation frequency

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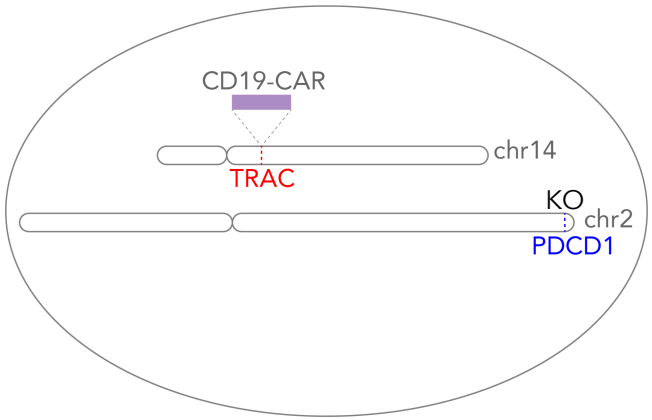
CB-010 is an allogeneic CAR-T cell therapy

PBMC donor-derived T cell



CB-010 is an allogeneic anti-CD19 CAR-T cell therapy to treat patients with B-cell malignancies

- AAV-mediated site-specific insertion of anti-CD19 CAR into TRAC locus
  - –This modification results in the knockout of the TCR to prevent graft vs host disease
- PDCD1 knockout
  - –This edit results in persistence of T cell polyfunctionality during tumor cell interaction
- chRDNA reagents used for editing reduce off-target frequencies

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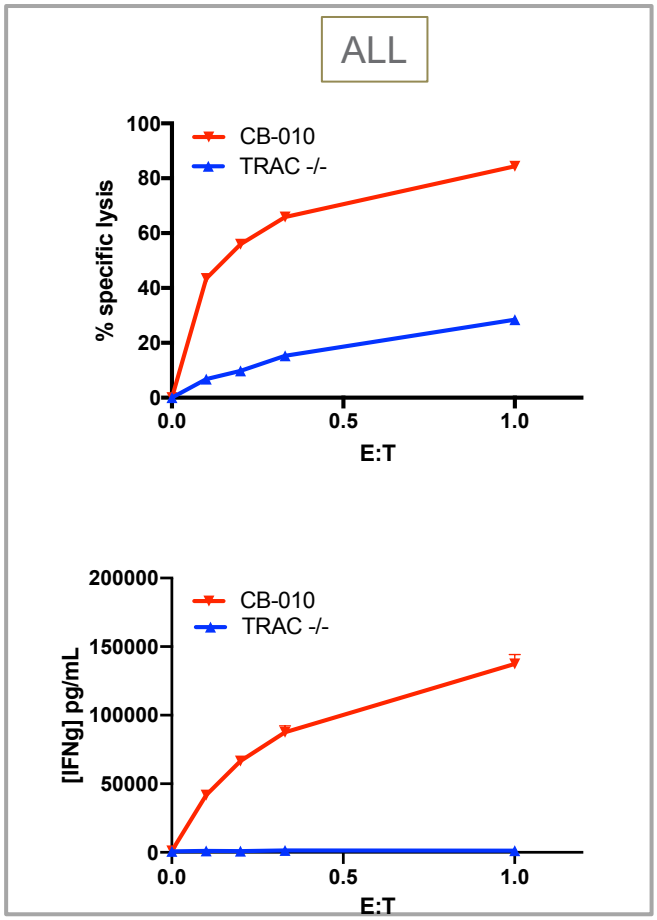
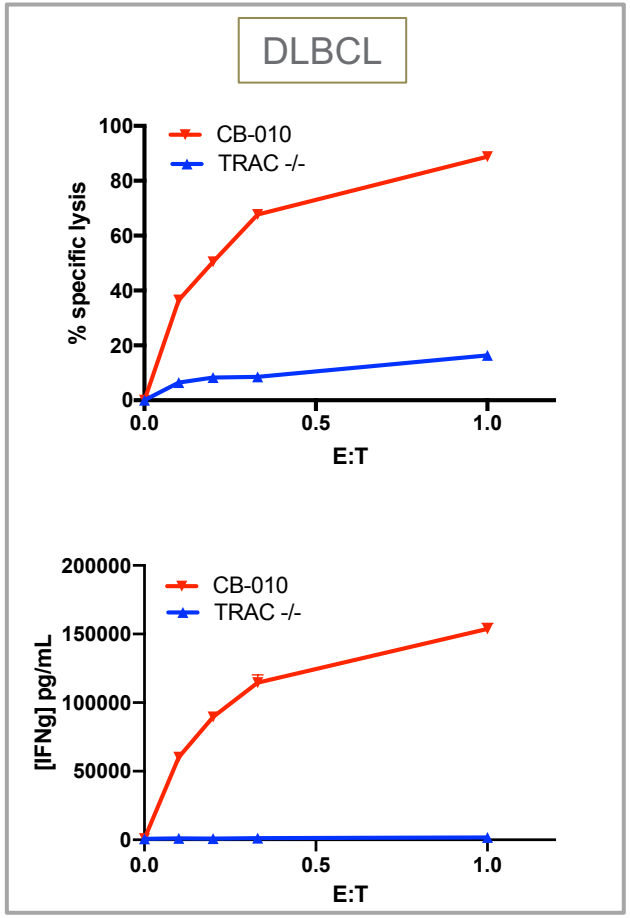
CB-010 *in vitro* cytotoxicity





CB-010 demonstrates specific *in vitro* cytotoxicity in models of ALL and DLBCL

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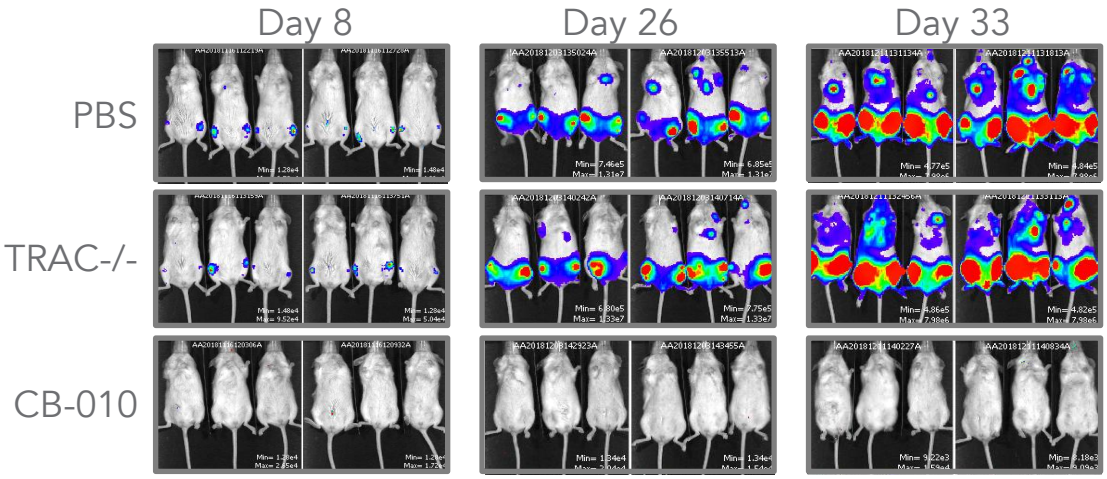
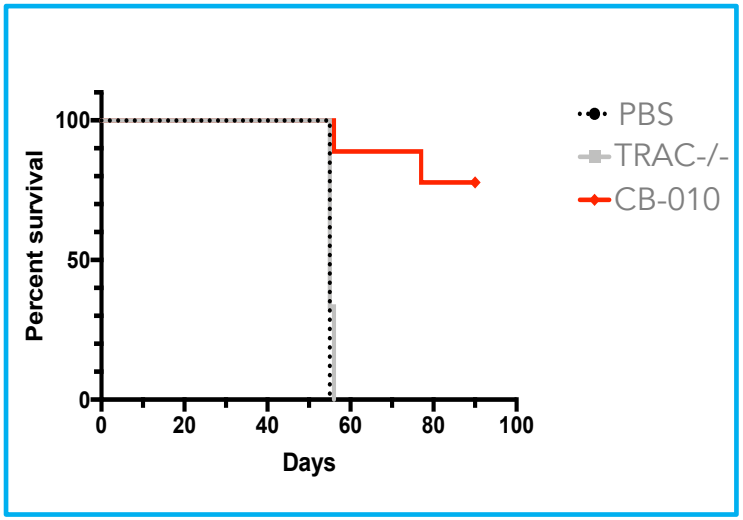
CB-010 *in vivo* efficacy

Nalm6_PD-L1 tumor cells were implanted orthotopically 5 days prior to CAR-T treatment





Reduction of tumor burden observed after
a single injection of allogeneic CB-010 CAR-T cells

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Summary

- Caribou chRDNA technology enables high efficiency, high specificity cell engineering in any cell type
  - Significantly improved specificity over traditional all-RNA systems
  - Compatibility with therapeutic engineering workflows including multiplex gene editing and site-specific donor insertion
  - Strong IP portfolio including 3 issued US patents related to Cas9 chRDNAs
- chRDNA technology is used for CB-010, an allogeneic anti-CD19 CAR-T cell engineered for enhanced function
- Other Caribou therapeutic platforms use chRDNA technology for novel engineering of additional immune cell therapies