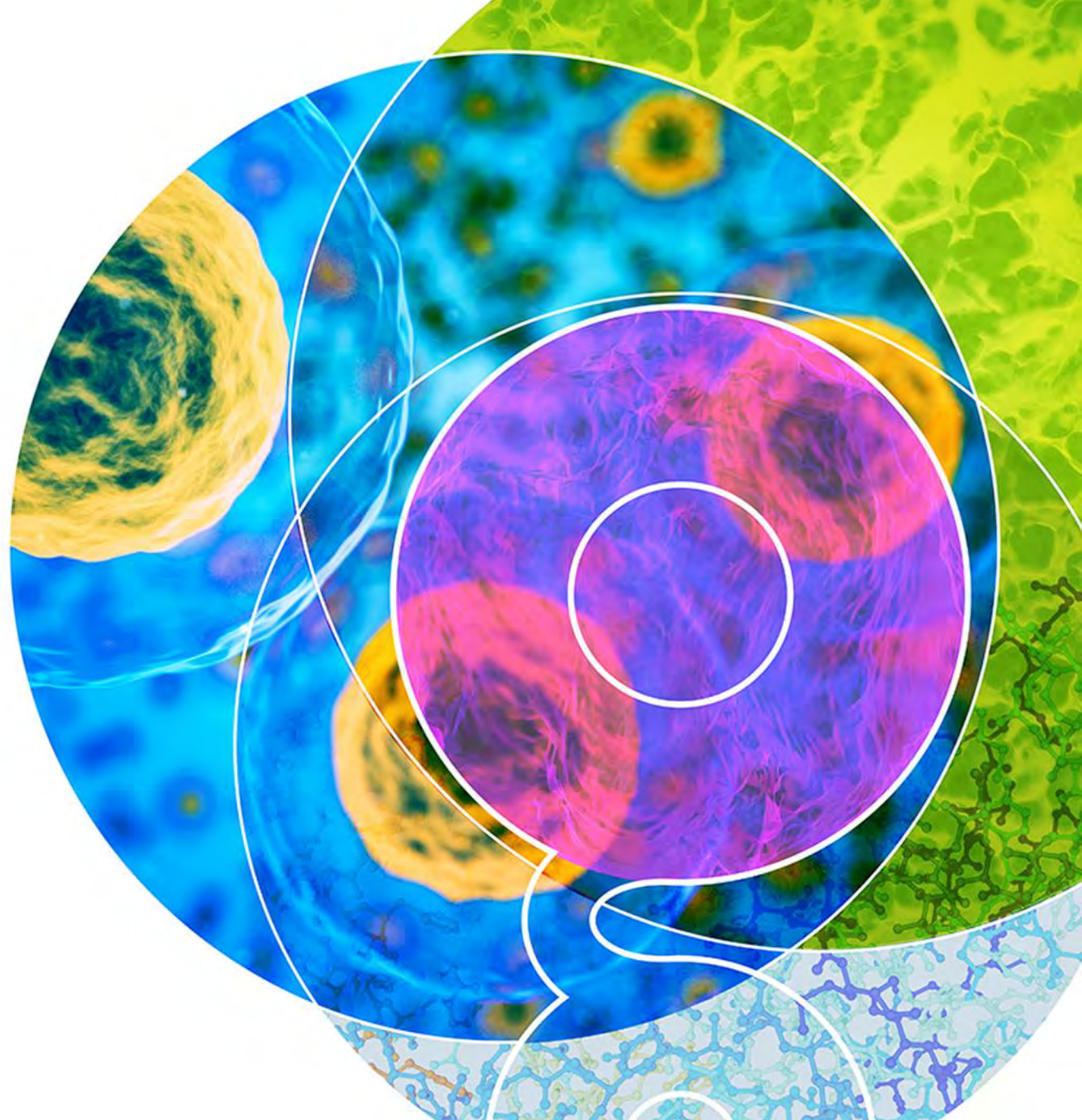




Robust immune evasion technology enables persistence of allogeneic cell therapies

iPSC Summit 2025

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Autoimmune diseases have significant global health impacts with high unmet medical need

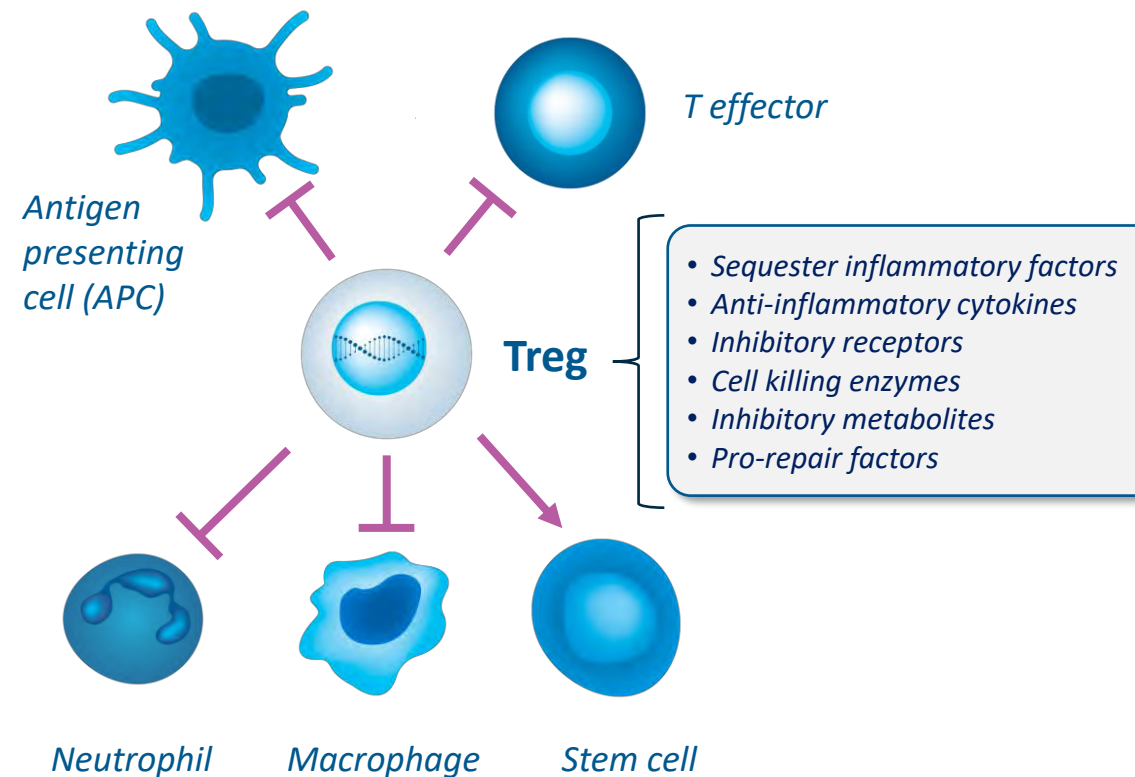
Regulatory T cells (Tregs) are critical for controlling inflammation and autoimmunity

Autoimmune Disease: significant global impact

- **100s of millions** affected globally
- **Significant impact** to lifestyle, long term health, and health economics
- **Underlying cause:** the body's immune system has turned against itself

Tregs – The Master Regulators

Tregs modulate the immune system via multiple mechanisms

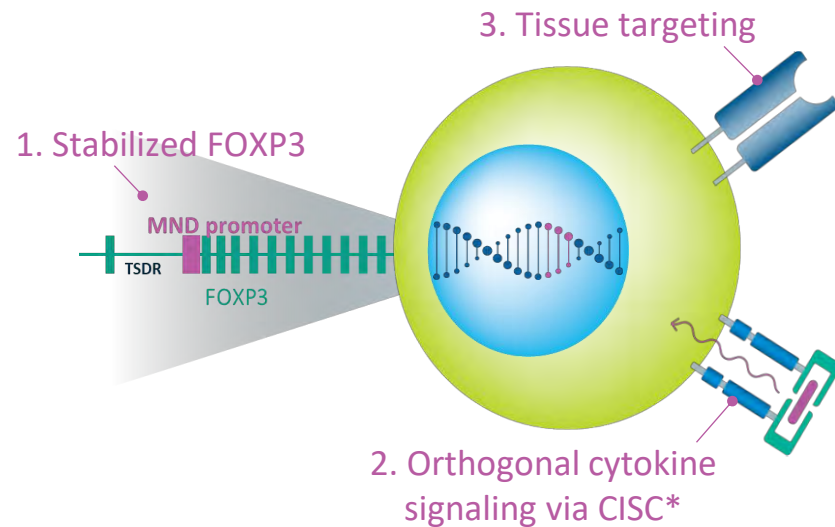


Genti's EngTregs – Highly stable & functional in the disease environment

EngTregs overcome the destabilizing disease environment that has defeated natural Tregs in patients with autoimmune disease

Genti EngTregs – resetting the body's immune system

- Leveraging Treg biology can lead to cures
- **EngTregs designed to succeed** where the body's natural Tregs have failed



- 1. Stability:** constitutive expression of FOXP3 locks-in Treg phenotype
- 2. Cytokine signaling:** CISC technology enables supportive IL-2 signaling in vivo to improve engraftment and function
- 3. Tissue targeting:** gets EngTregs to site of disease

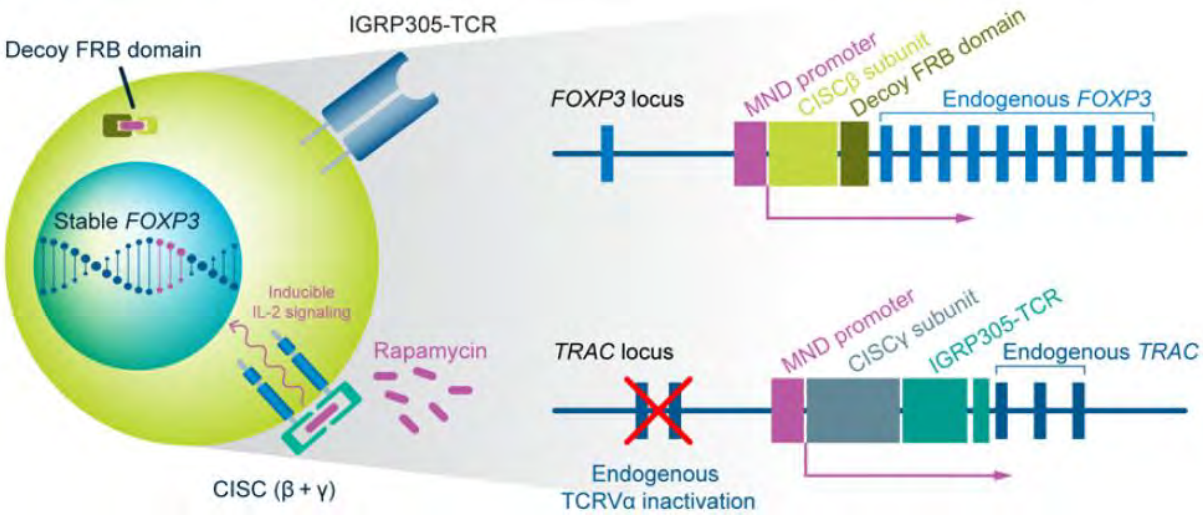
*CISC = chemically-induced signaling complex

Highly scalable manufacturing platform resulting in stable Tregs without complex sorting

Only dual edited cells express full CISC; which are selected for during manufacturing in the absence of IL-2 and presence of rapamycin

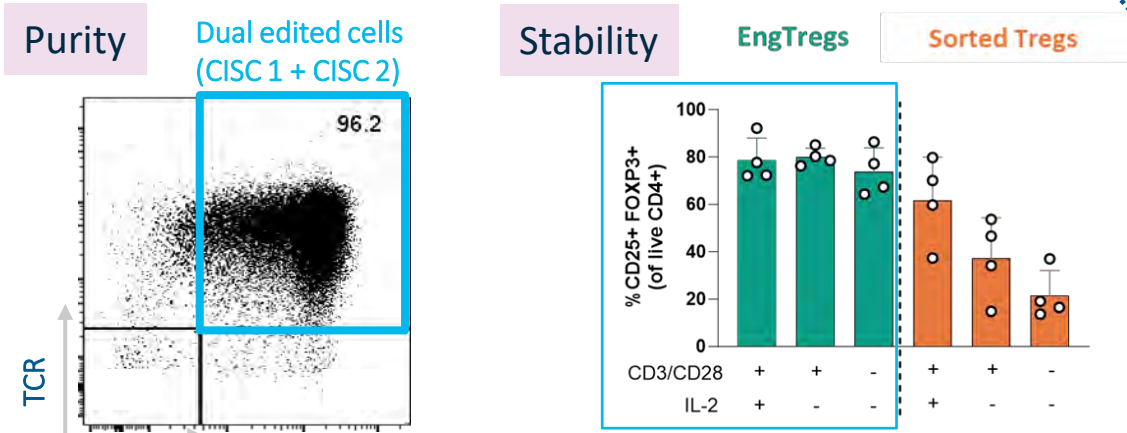
Dual Editing Enables Scalable Production of Pure EngTregs from CD4 Cells

Example: lead asset GNTI-122 for T1D

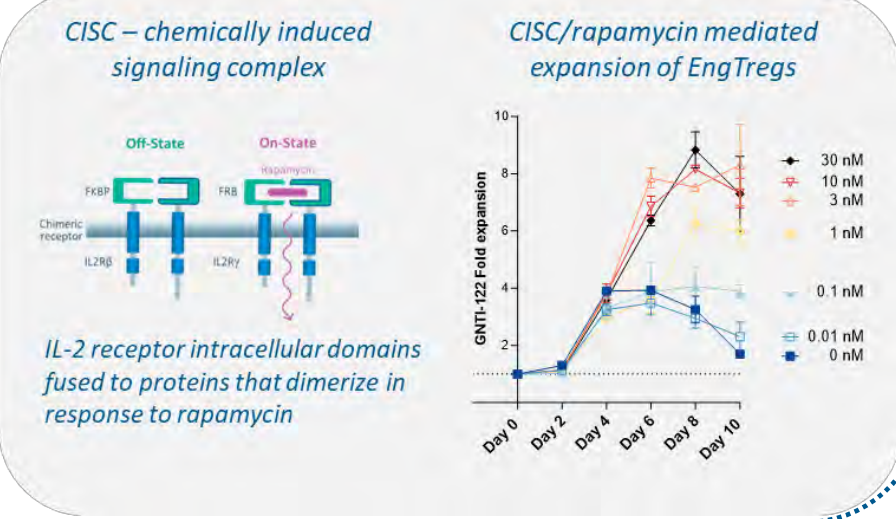


Uenishi et al. 2024. JCI Insight.

EngTreg is stable and pure

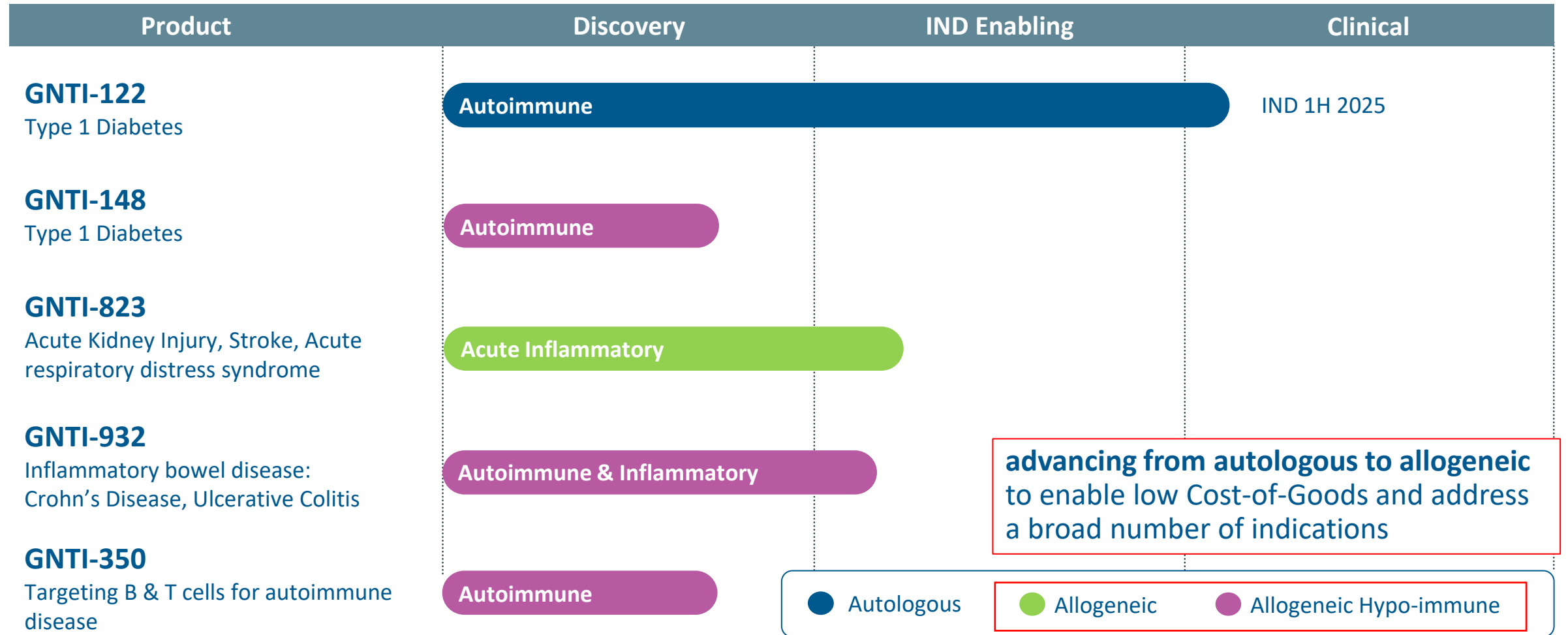


Scalability and Cytokine Support

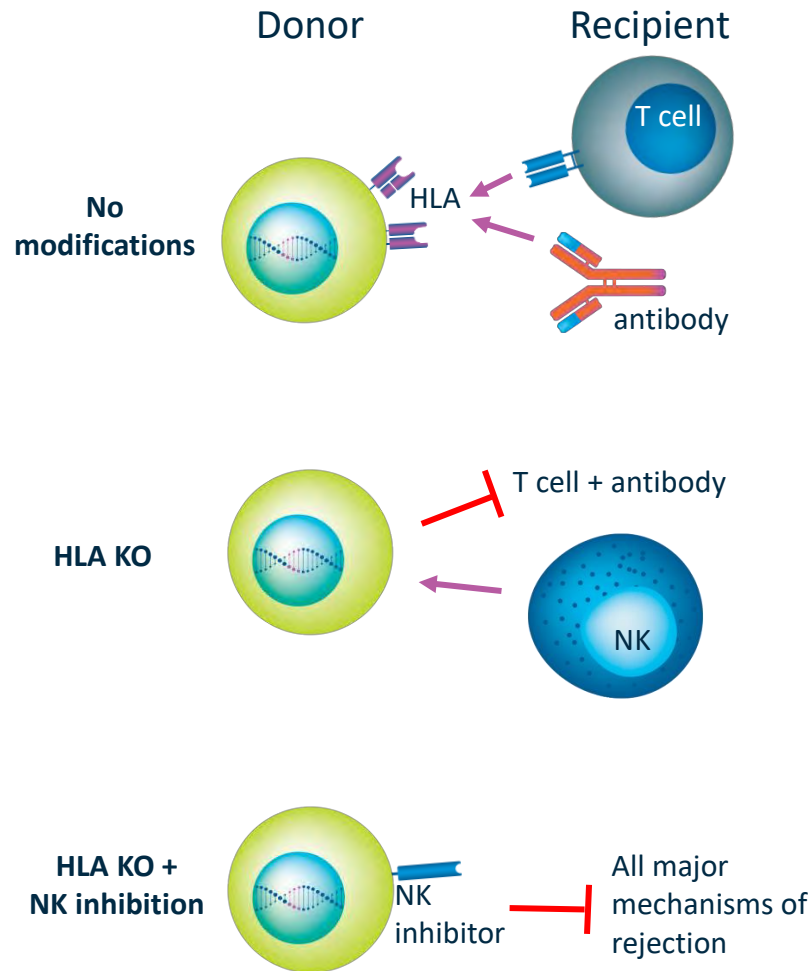


Genti pipeline: Advancing into the clinic in 2025

Multiple assets poised to generate clinical data within the next several years



Rejection of therapeutic cells by host immune system is a major barrier for allogeneic cell therapies

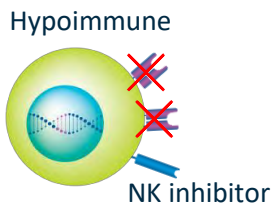
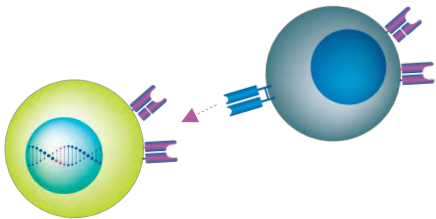
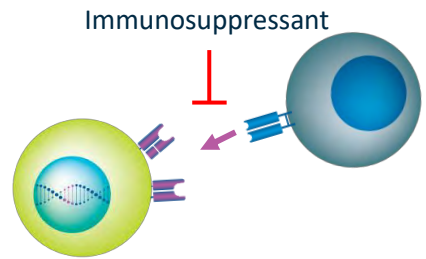


Recipient T cells and antibodies mediate rejection of allogeneic cells by targeting mismatched donor HLA
Memory T cell and antibody responses also prevent re-dosing

HLA KO can avoid T cell and antibody rejection but natural killer (NK) cells reject HLA-deficient cells

HLA KO combined with an effective NK inhibitor can mitigate T cell, antibody, and NK mediated rejection

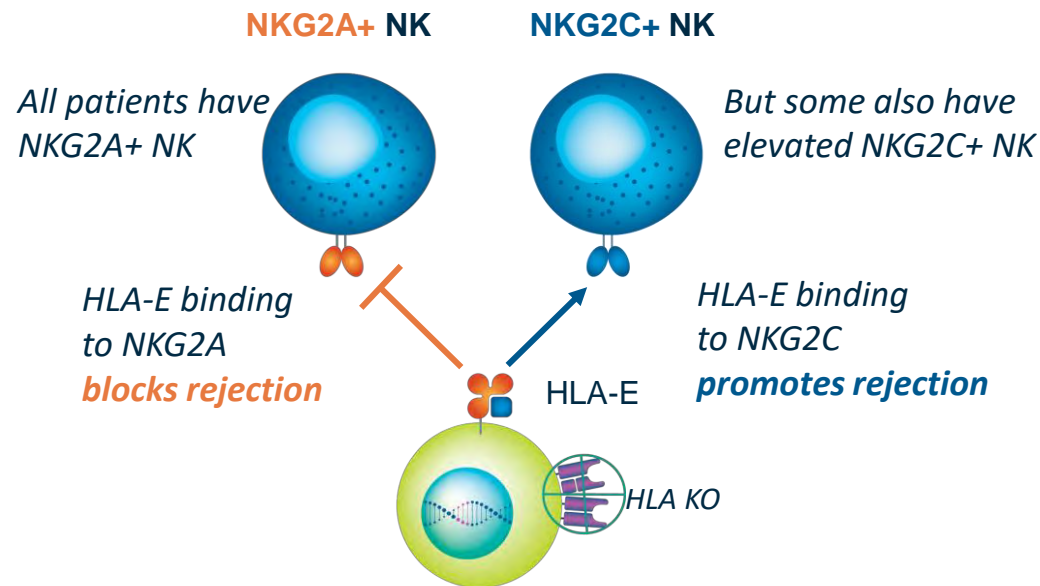
General approaches to addressing rejection of allogeneic cells



Approach	Mechanism	Benefits	Drawbacks
Immune suppression	<ul style="list-style-type: none"> Suppress host immune rejection response with varying selectivity 	<ul style="list-style-type: none"> Easy to implement; solutions readily available (e.g., lymphodepletion) 	<ul style="list-style-type: none"> Toxicities from broad immune suppression
HLA (partial) matching	<ul style="list-style-type: none"> Rely on banking multiple donors and matching patient HLA to the appropriate donor HLA 	<ul style="list-style-type: none"> Lower risk of rejection with increasing matched HLA alleles 	<ul style="list-style-type: none"> Still susceptible to minor antigen mediated rejection Logistically challenging Higher cost due to more batches required
HLA KO + NK inhibition	<ul style="list-style-type: none"> Avoid major mechanisms of immune rejection 	<ul style="list-style-type: none"> No immune suppression or complex logistics required Re-doseable 	<ul style="list-style-type: none"> Lack robust solutions

Examples of clinical stage NK inhibitor for hypimmune allogeneic cells

HLA-E

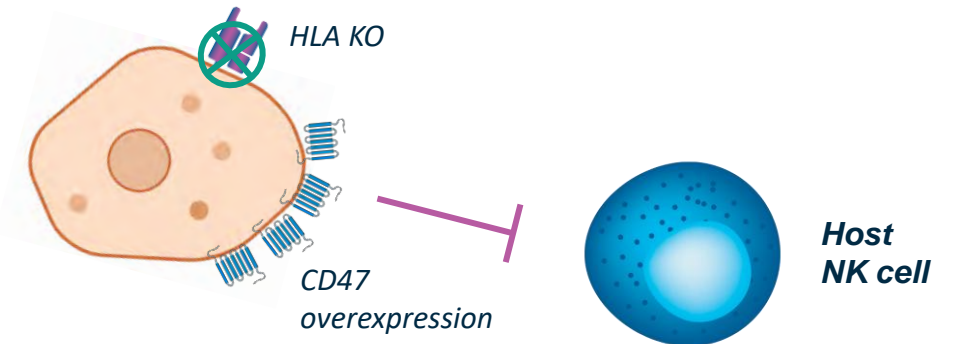


Drawback

- Unlikely to provide long-term protection in some patients due to its dual NK inhibitory (NKG2A) and activating (NKG2C) effects

CD47

Mechanism: Strong overexpression of CD47 engages inhibitory receptor SIRPα

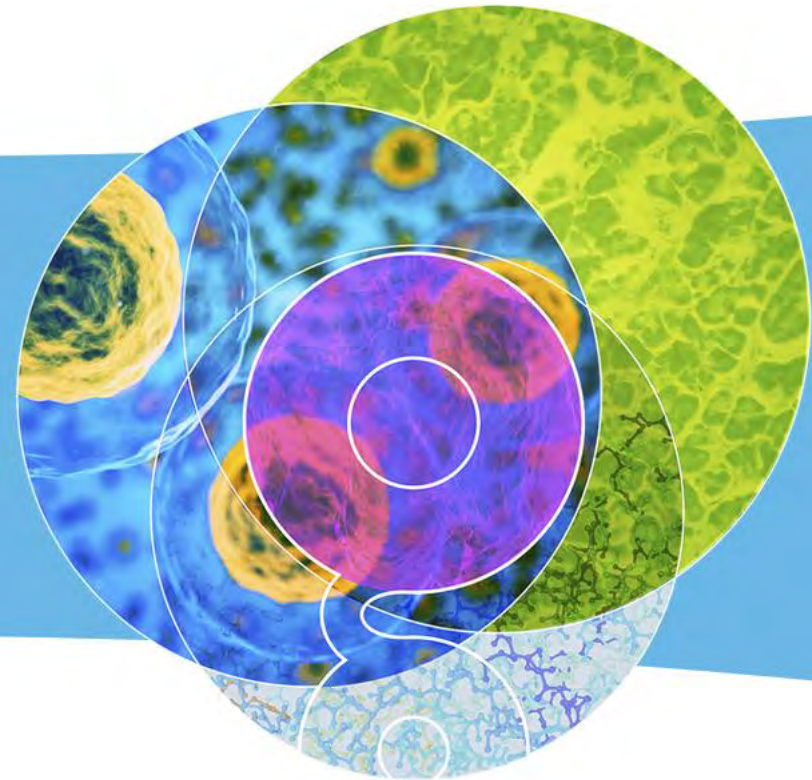


Drawback

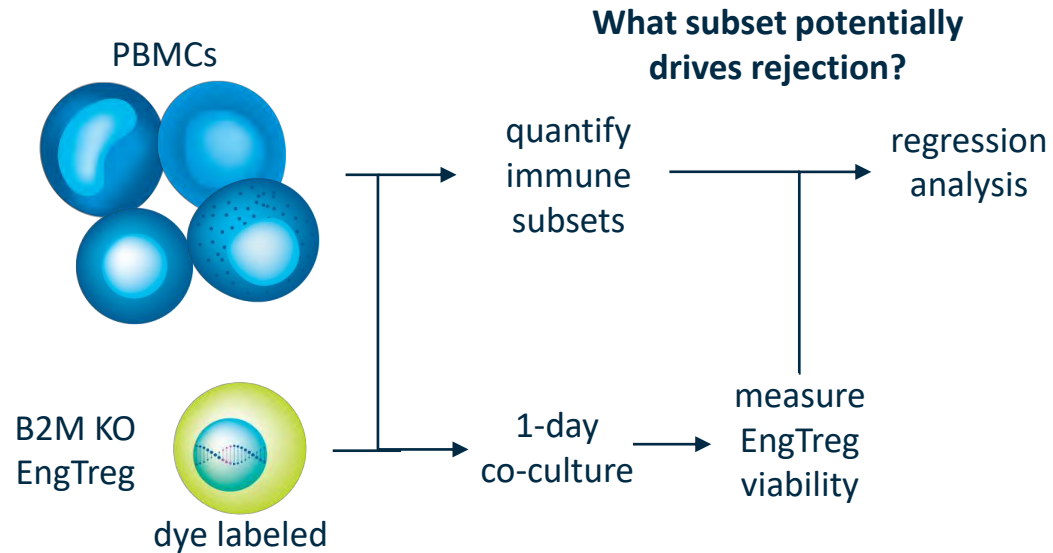
- Lack consistent NK inhibitory effect across cell types and therapeutic contexts

Wang et al, 2021, Nat Biomed Eng
Zhang et al, 2024, Blood Adv
Pizzato et al, 2024, Stem Cell Rep
GentiBio internal data

Finding a robust NK inhibitor for hypimmune applications



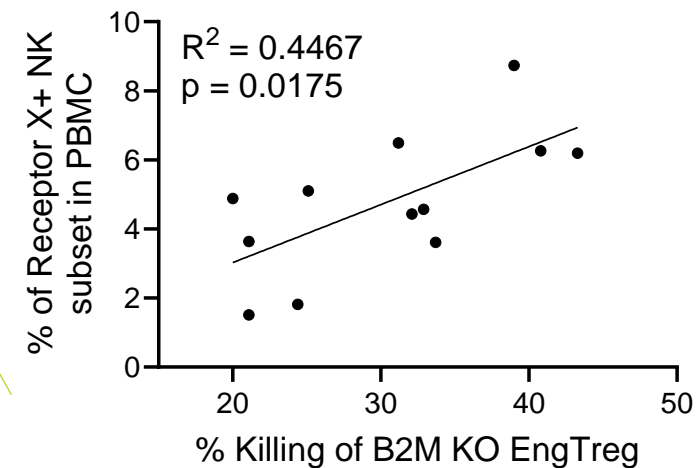
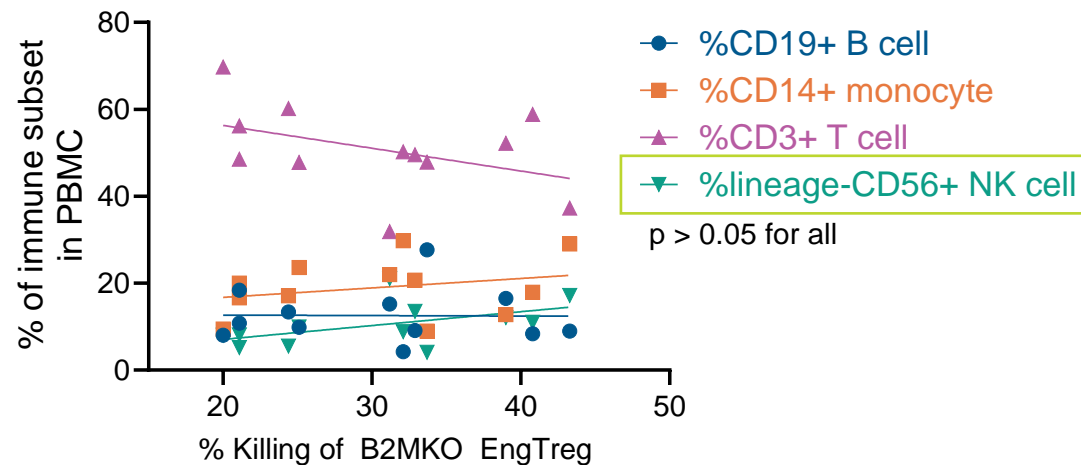
Rejection of B2M KO EngTreg is significantly related to the frequency of “Receptor X”+ NK cells in PBMCs



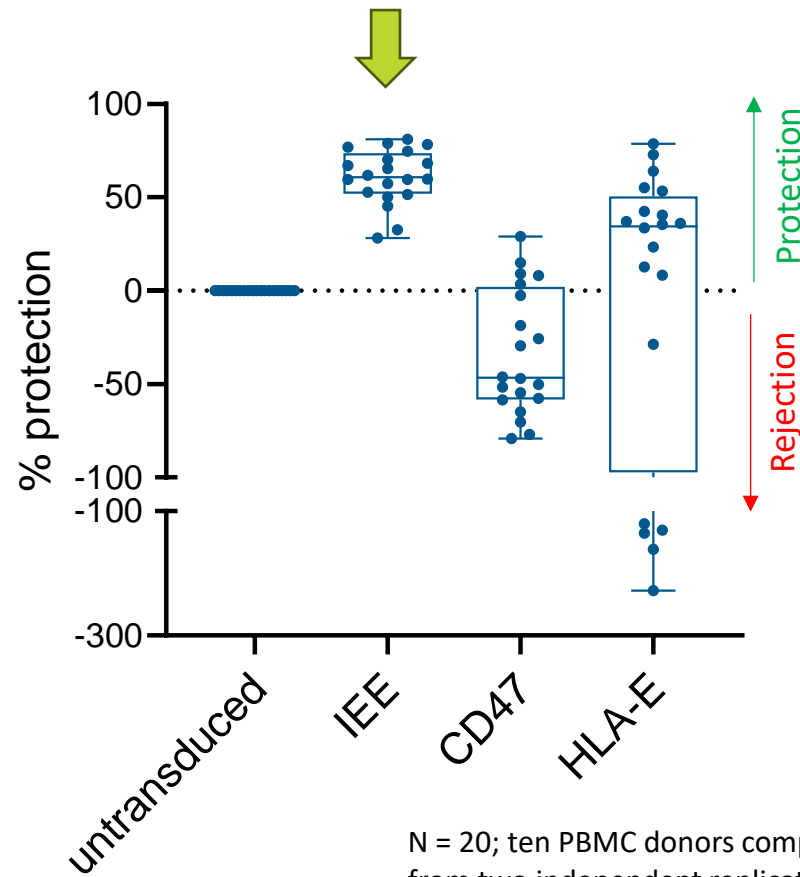
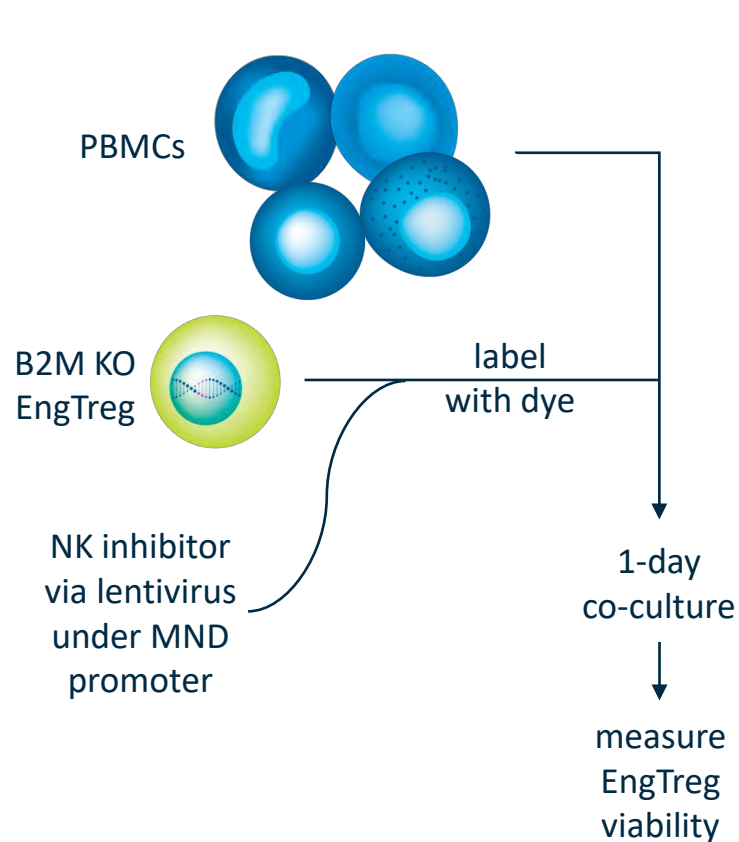
Killing of B2M KO EngTreg was only significantly related to the frequency of “Receptor X”+ NK cells in PBMCs, not total NK cells

No significant relations with other human NK subsets were observed (not shown)

Inhibiting Receptor X+ NK cells is sufficient?



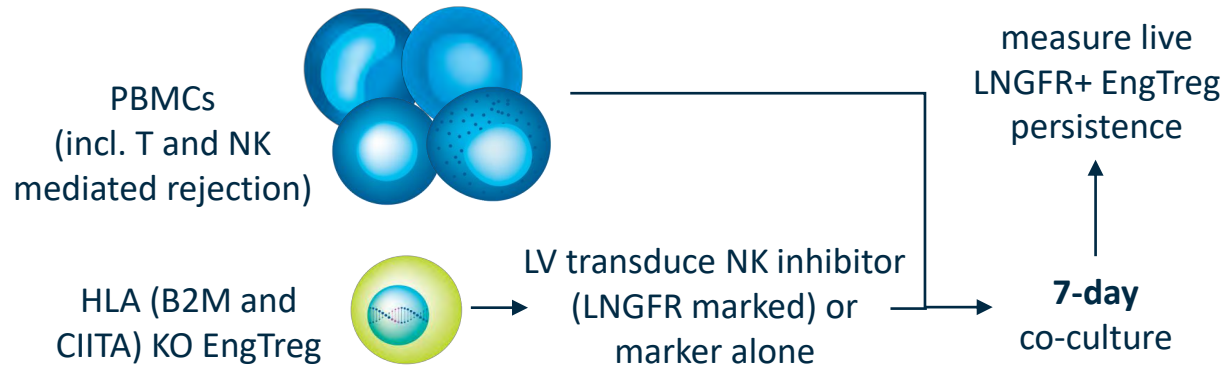
Expression of a Receptor X ligand (IEE) protected B2M KO EngTreg from PBMC killing and consistently conferred higher protection than field standard NK inhibitors



N = 20; ten PBMC donors compiled from two independent replicates. Median \pm range shown.

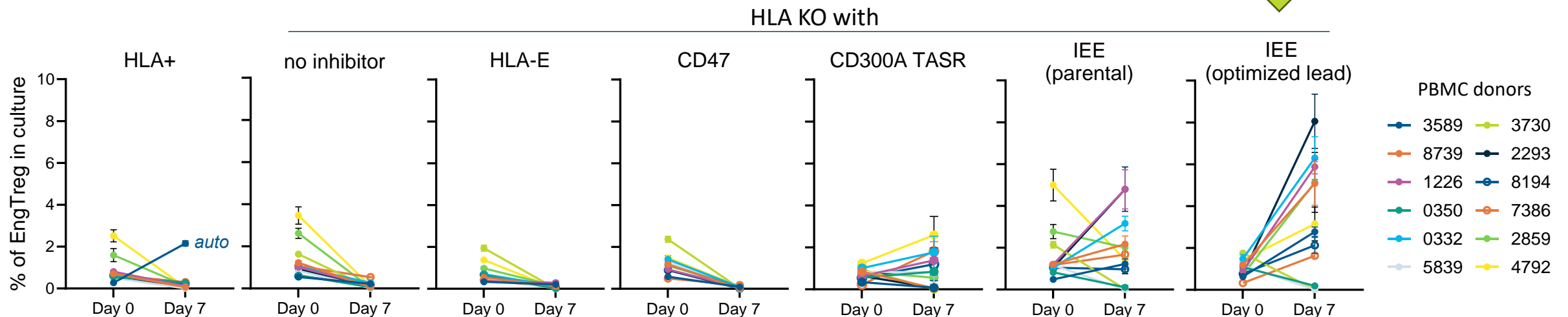
Gentibio's Immune Evasion Engineering (IEE), a Receptor X ligand, offers consistently better protection than CD47 and HLA-E

Optimized IEE outperforms field standard and emerging NK inhibitors in a rigorous 7-day in vitro rejection assay system



An optimized IEE enabled higher persistence than competing technologies in side-by-side comparisons after 7 days of culture

The lack of observable protection by HLA-E in this assay suggests a highly aggressive rejection system



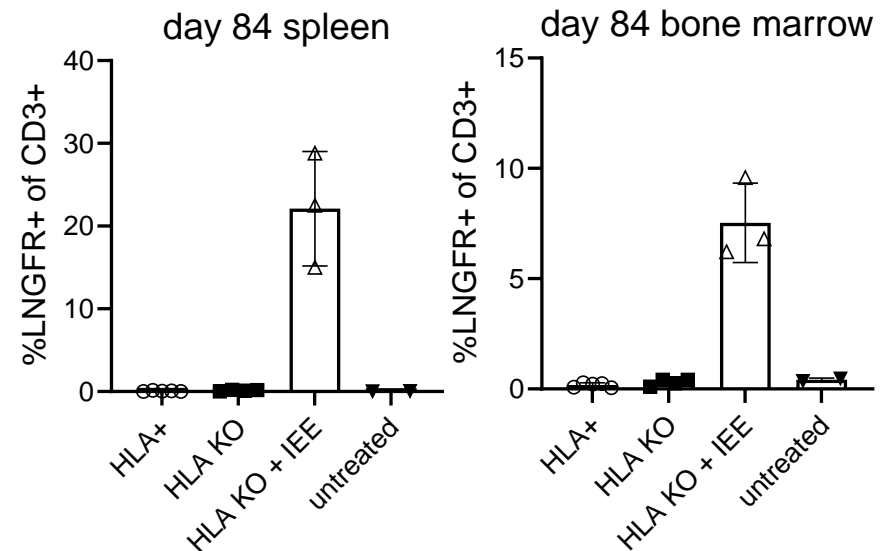
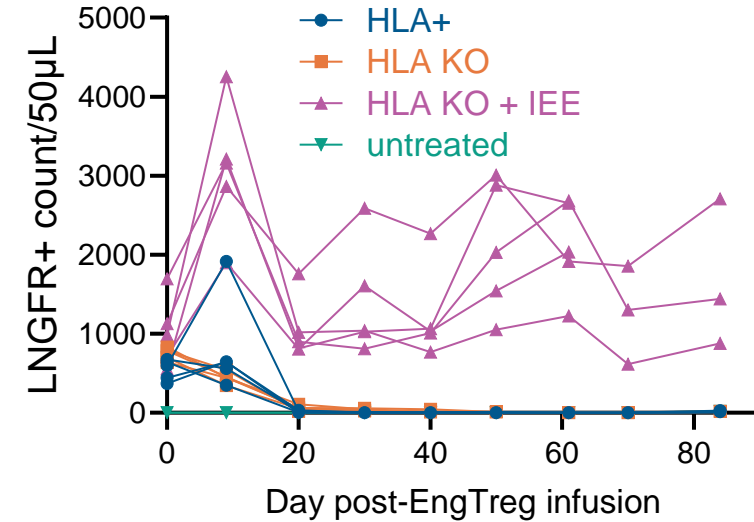
N = 12 PBMC donors. Mean \pm SD of triplicates shown. Frequency of live, CD14⁻ cells were quantified. Similar trend observed based on counts (not shown).

Optimized IEE enabled in vivo persistence for 12 weeks in a CD34+ HSC humanized NSG-hIL15 mouse model

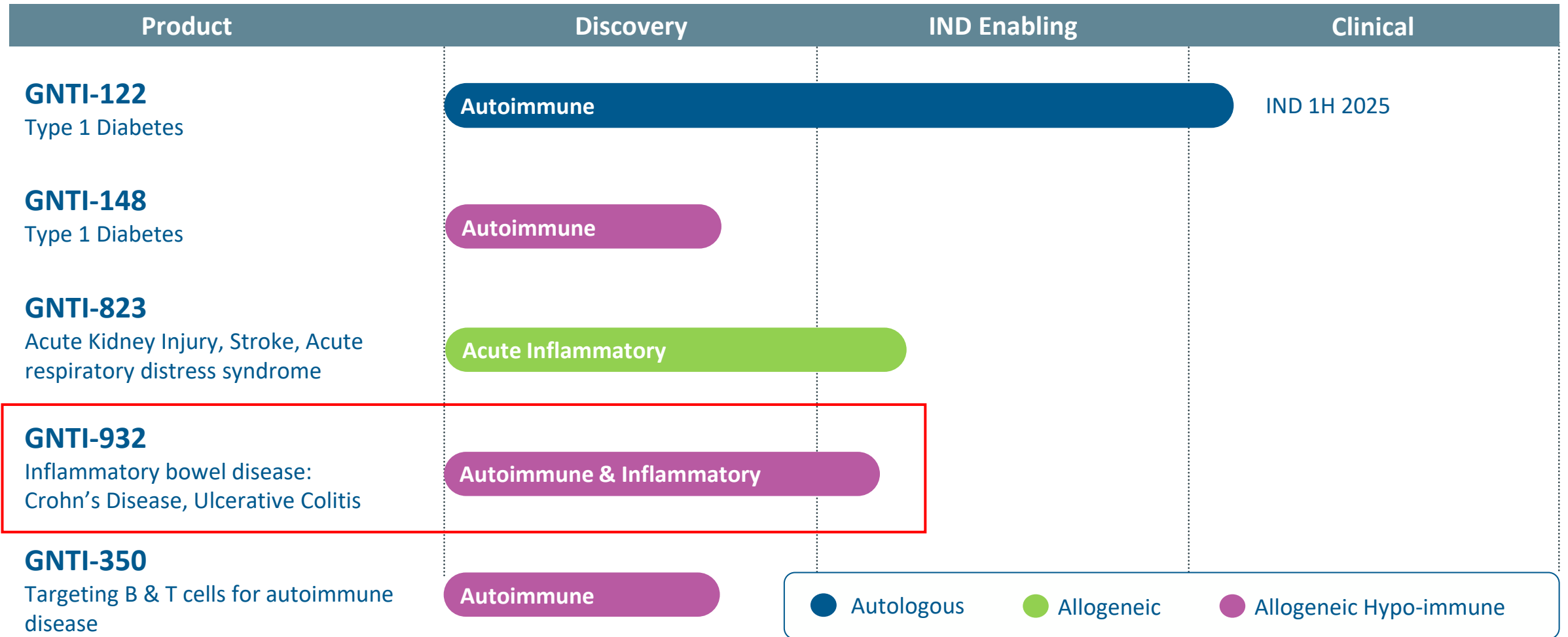
n	Test article (LNGFR marked)	Host
5	Allogeneic EngTreg, HLA+	CD34+ HSC humanized NSG-hIL15 (~12-weeks post-HSC)
5	Allogeneic EngTreg, HLA KO	
5	Allogeneic EngTreg, HLA KO + IEE	
2	Untreated	



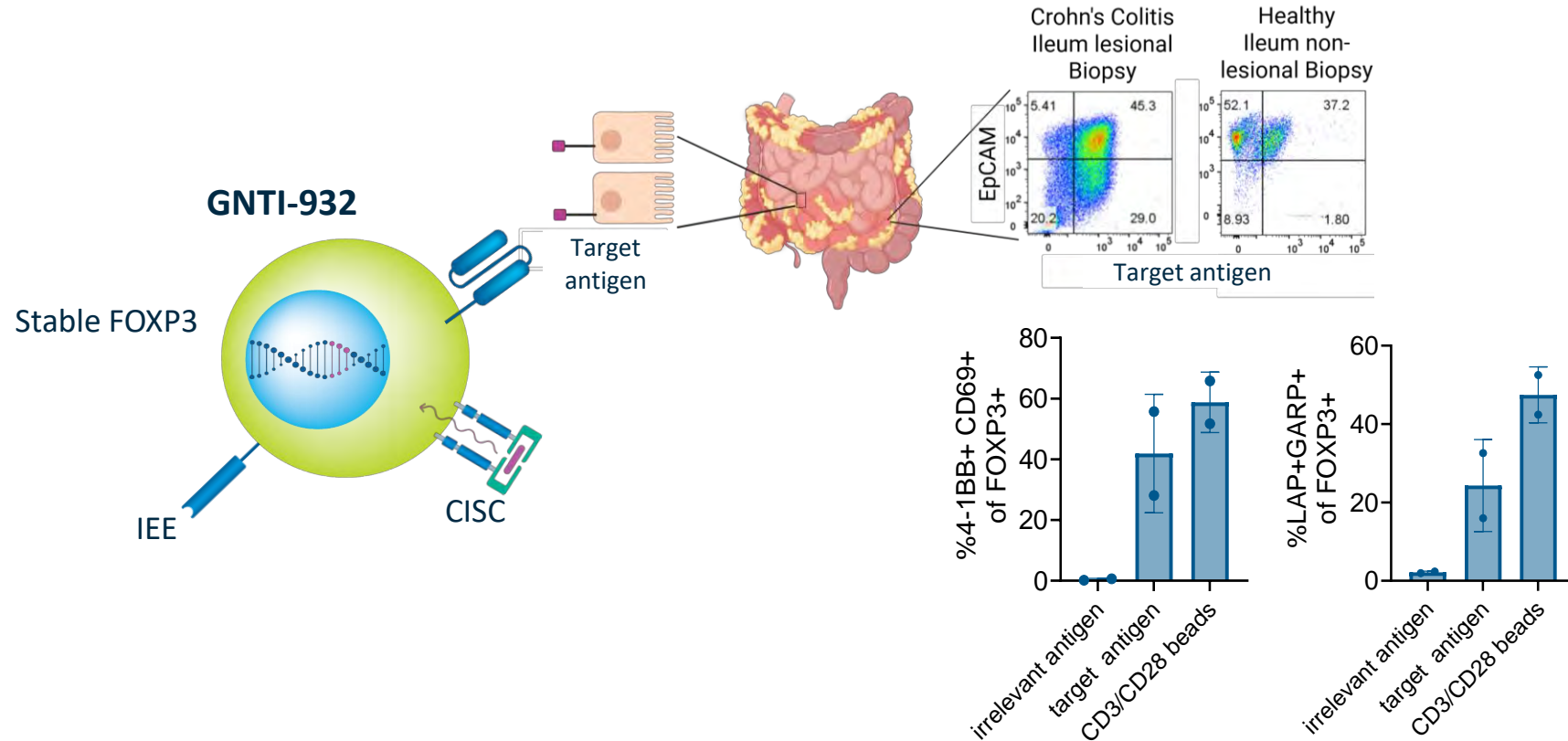
- Sampled peripheral blood ~every 10 days
- Supported EngTreg persistence with rapalog (activate CISC)
- Analyzed bone marrow and spleen at final take-down



Multiple assets in development incorporate IEE technology



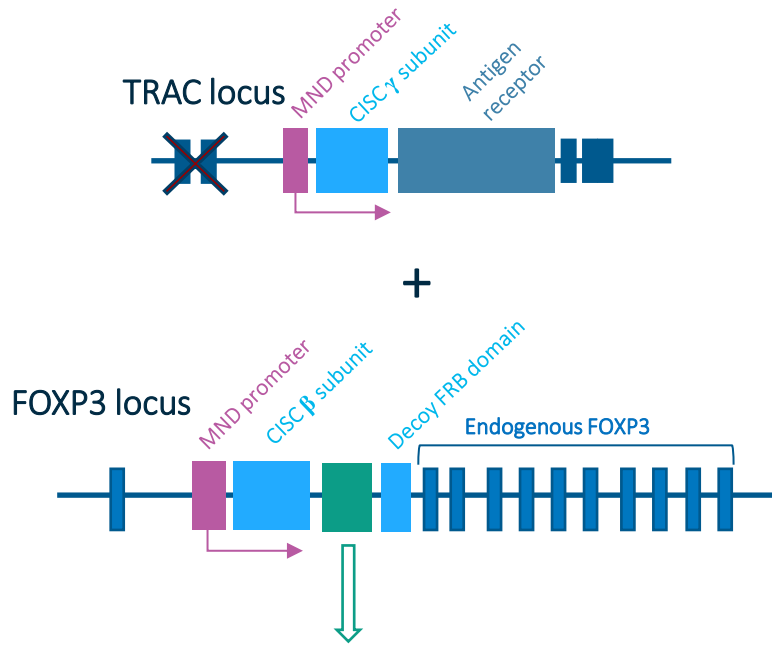
GNTI-932: gut-specific EngTreg therapy to treat inflammatory bowel disease



- Targets a gut-specific antigen for treating IBD
- Built on core technology of stable FOXP3 and CISC cytokine support
- Allogeneic asset with HLA KO + IEE hypimmune technology enabling long-term persistence

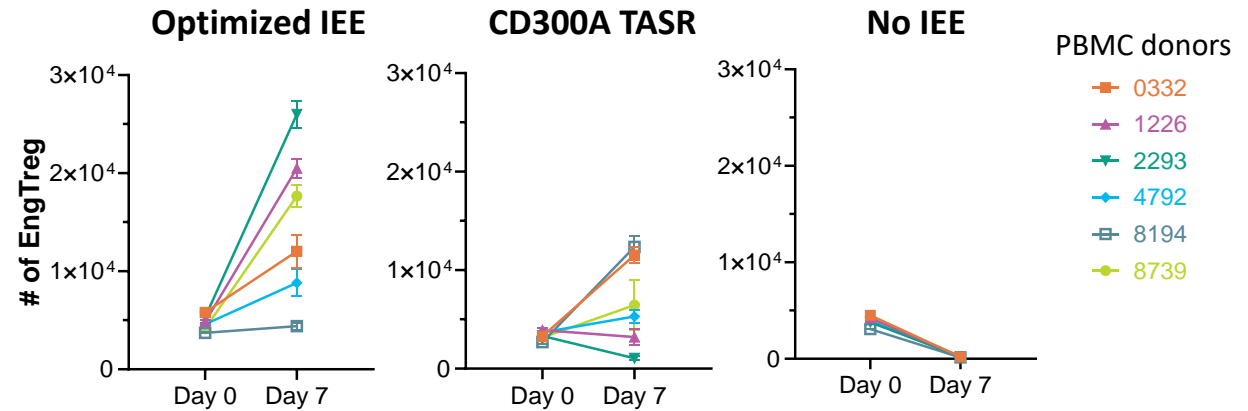
IEE similarly protected HLA KO EngTreg when knocked-in at FOXP3

Cell engineering method



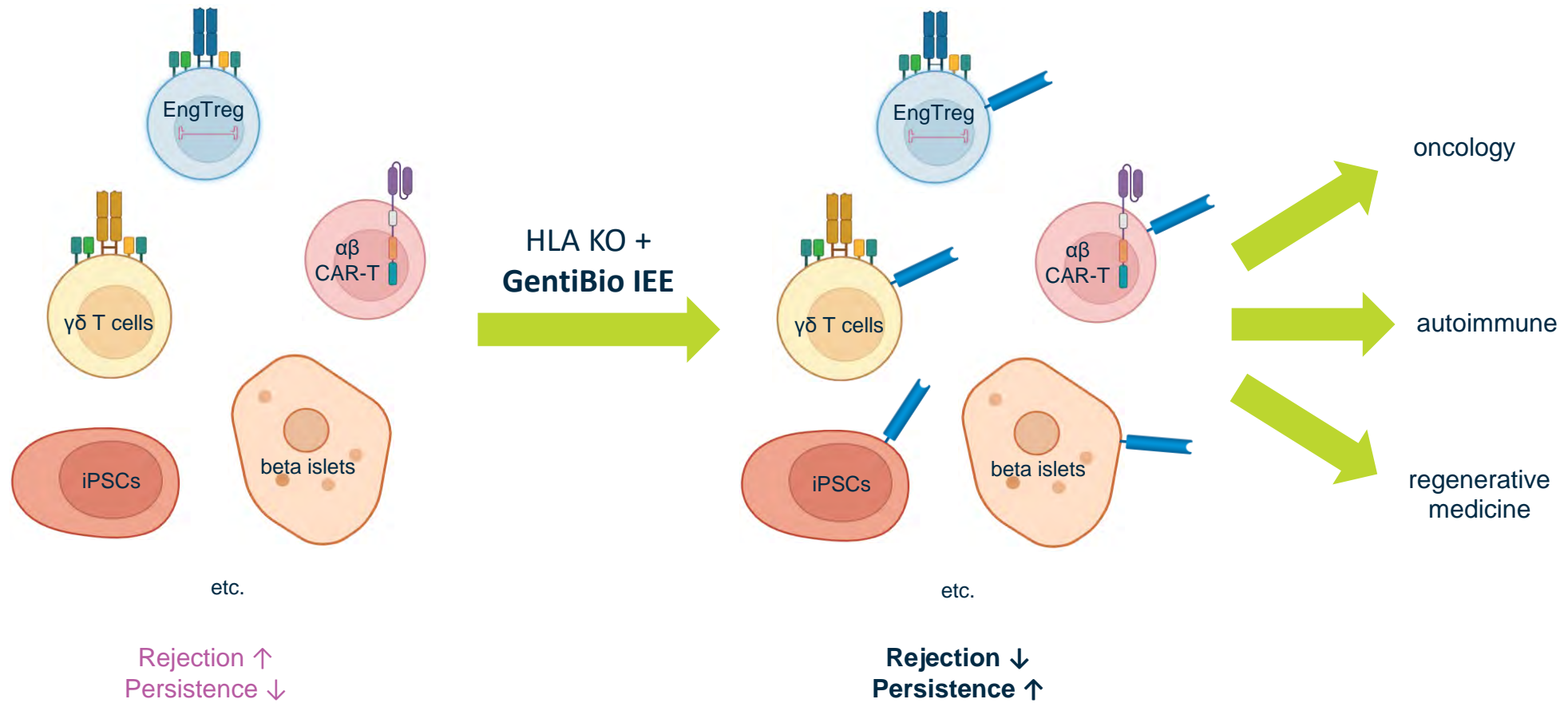
1. GentiBio optimized IEE
2. CD300A TASR
3. No IEE

In vitro 7-day rejection assay

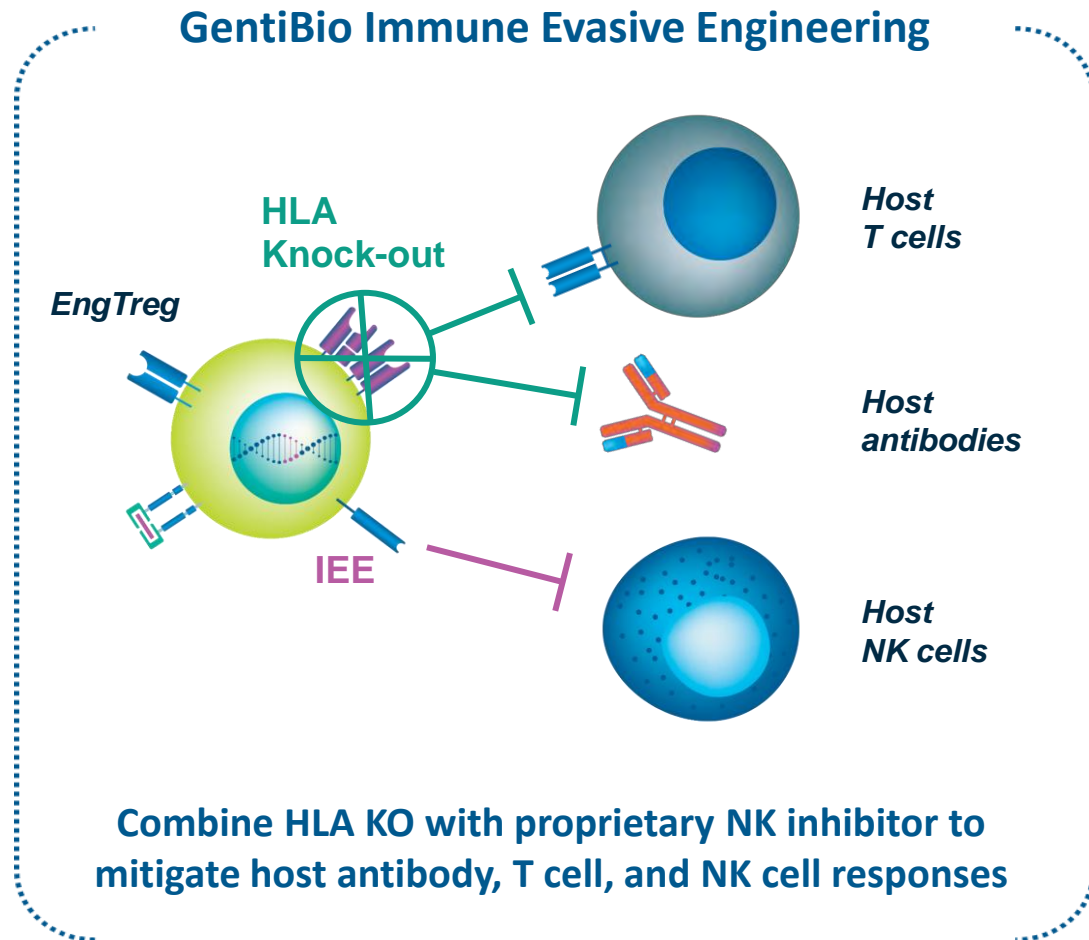


IEE effect is consistent when expressed from knock-in at FOXP3 (here) or lentivirus (previous slides)

Application to other cell types



GentiBio IEE technology enables hypoimmune allogeneic cell therapies for long-term persistence



GentiBio IEE technology enables:

- superior persistence to industry approaches that have been incorporated into clinical products
- next generation allogeneic EngTreg products to treat IBD, T1D, and B cell driven disease
- allogeneic cell approaches including CAR-T or iPSC-based products for improved persistence and efficacy