Bill, living with transthyretin amyloidosis, and his wife, Maura

A Novel Strategy for Off-the-shelf T Cell Therapies Evading Host T Cell and NK Cell Rejection

Yong Zhang, Ph.D.

European Society of Gene and Cell Therapy Annual Congress

October 20, 2021

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Disclosure: Employee of Intellia Therapeutics, Inc

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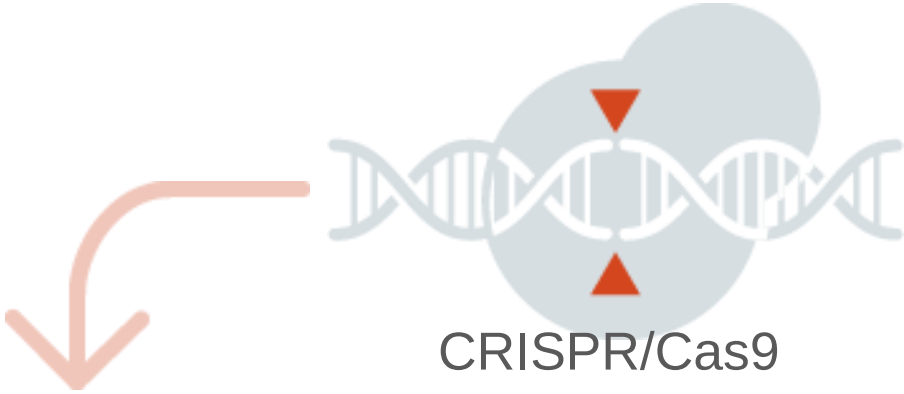
Building a Full-Spectrum Genome Editing Company



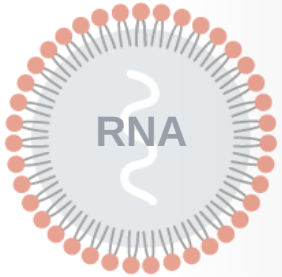
CRISPR/Cas9

In Vivo

CRISPR is the therapy

Genetic diseases

LNP



Modular Platform

CELL

Ex Vivo

CRISPR creates the therapy

Immuno-oncology

Autoimmune diseases

LNP: Lipid Nanoparticle

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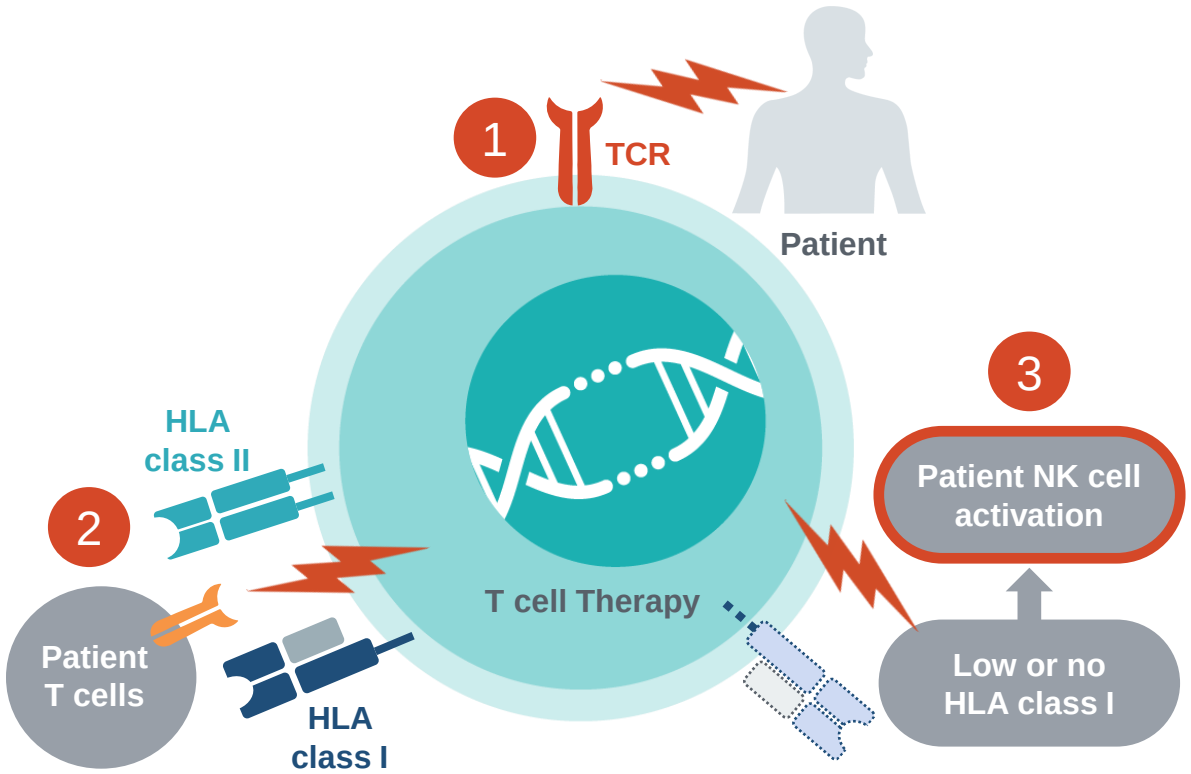
Three Immune Concerns Must Be Addressed by Allogeneic Cell Therapies



1

Graft versus host disease (GvHD)

T cell receptor (TCR) from allogeneic T cells recognizes and kills recipient (host) cells.

Largely solved with knockout (KO) of endogenous TCR

2

Rejection via host T cells

Human Leukocyte Antigen (HLA) molecules must match between donor and recipient to prevent rejection from:

- Host CD8 (HLA class I) T cells
- Host CD4 (HLA class II) T cells

3

Rejection via host natural killer (NK) cells

NK cells will attack cells that lack HLA-I expression or have low HLA-I

No validated solution yet

HLA-I / II: Human leukocyte antigen class I / II

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Immune Concerns Unaddressed by Current Allogeneic Solutions

Approach	Employ intense lymphodepletion regimen	Knockout (KO) HLA-I (B2M)	KO HLA-I & express NK inhibitor (HLA-E)	**Intellia's Approach** KO HLA-II & Receptor X*
Avoid rejection of cell therapy by host CD8 T cells	✓	✓	✓	✓
Avoid rejection of cell therapy by host CD4 T cells	✓	✗	✗	✓
Avoid rejection of cell therapy by host NK cells	✓	✗	✗	✓
Avoid profound immunosuppression	✗	✓	✓	✓

*Receptor X: Undisclosed target
B2M: Beta-2-microglobulin
HLA-E: Human leukocyte antigen class E

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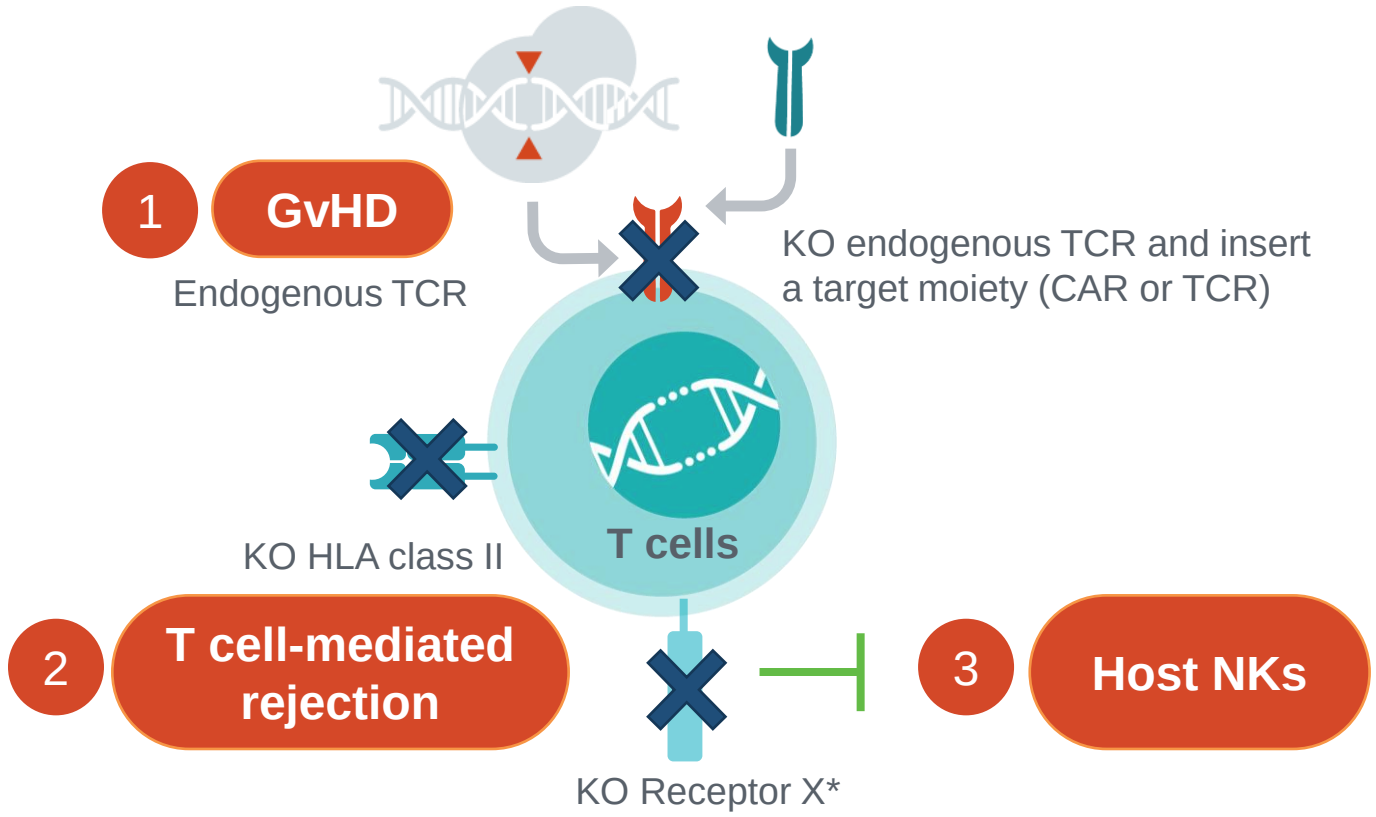
Intellia's Differentiated Allogeneic Approach Aims to Address All Three Immune Concerns



Key Advantages

- Approach is applicable to CAR and TCR
- Solves for host NK and T cell rejection
- Avoids long-term immunosuppression

*Receptor X: Undisclosed target

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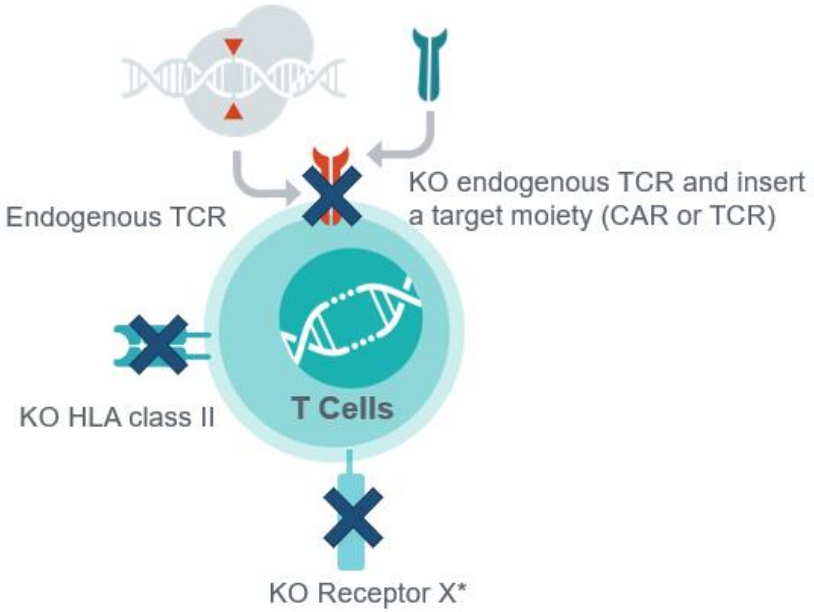
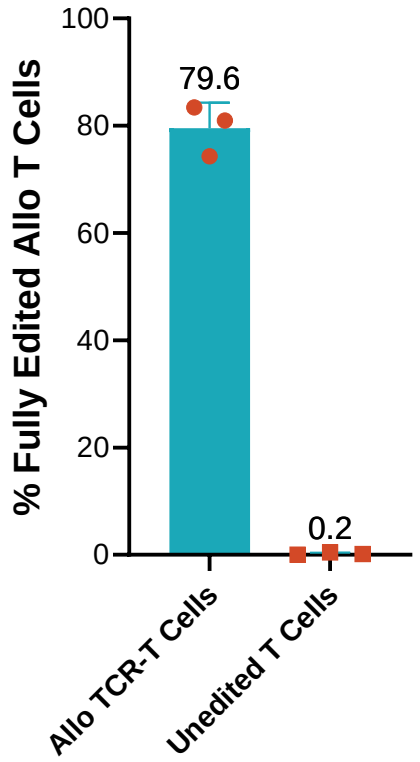
Achieved High Editing Efficiency in Allo TCR-T Cells and Allo CAR-T Cells by Leveraging Our Proprietary Multiplex Editing Platform





Allo TCR-T Cells (4 KOs + Insertion) ~80% final yield

- Viability: 98.1% (N=3)
- Expansion: 279.5-fold (N=3)

Each dot represents one donor

- Editing efficiency for each gene target (≥95%) allows for ~80% final yield of engineered TCR-T cells with all edits
- Similar high yield (~86%) was observed in Allo CAR-T cells (data not shown)
- Intellia's proprietary sequential editing platform minimizes translocations between on-target loci
  - Refer to Intellia's presentation by Dr. Aaron Prodeus (Poster P205) for more information on the platform

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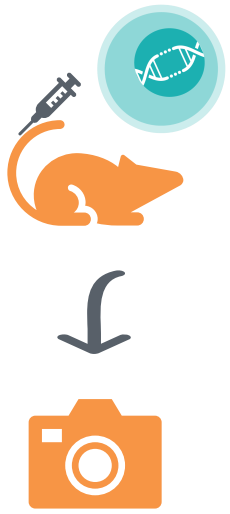
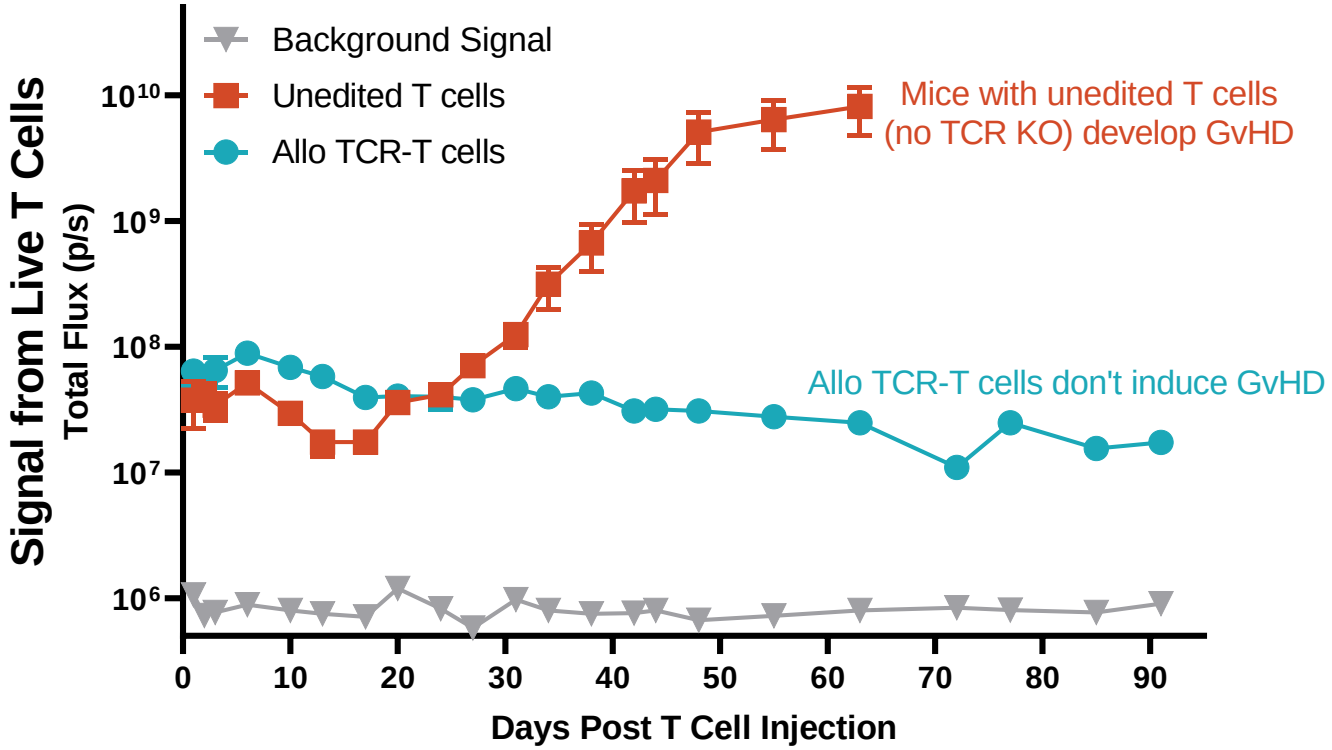
1 No GvHD Detected in Mice Engrafted with Allo TCR-T Cells

Luciferase+
Unedited or Allo T cells



IVIS imaging to detect
Luciferase+ T cell signal



- After exposure to host (mouse, xeno) antigens, Allo TCR-T cells do not show uncontrolled proliferation, and mice are protected from GvHD in contrast to unedited T cells
- Allo T cells persist for at least 90 days in recipient mice

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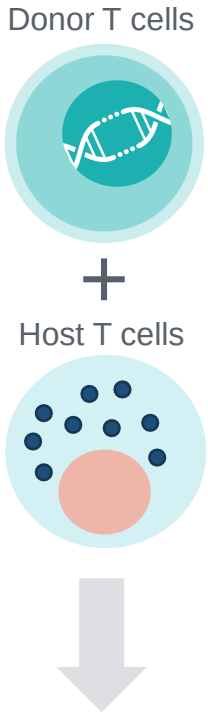
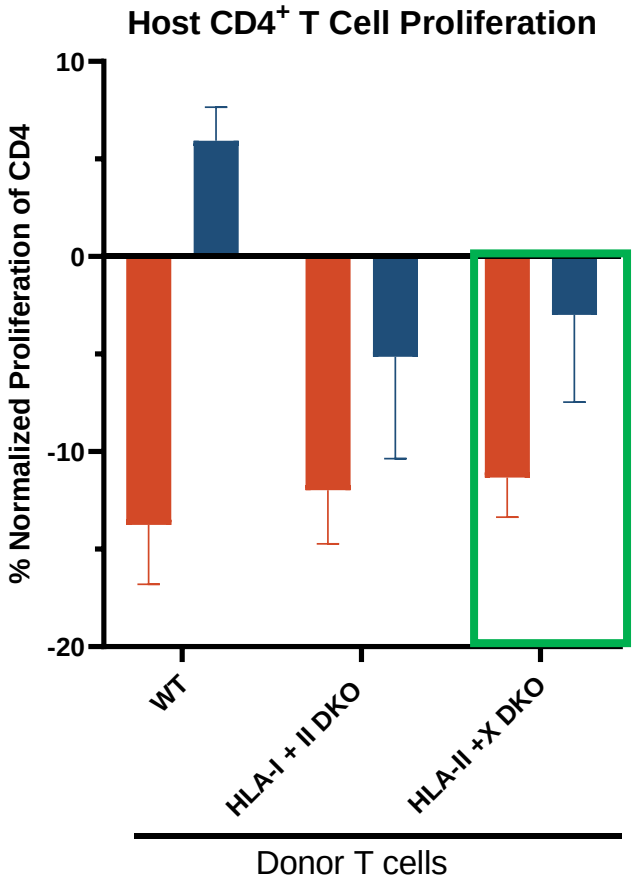
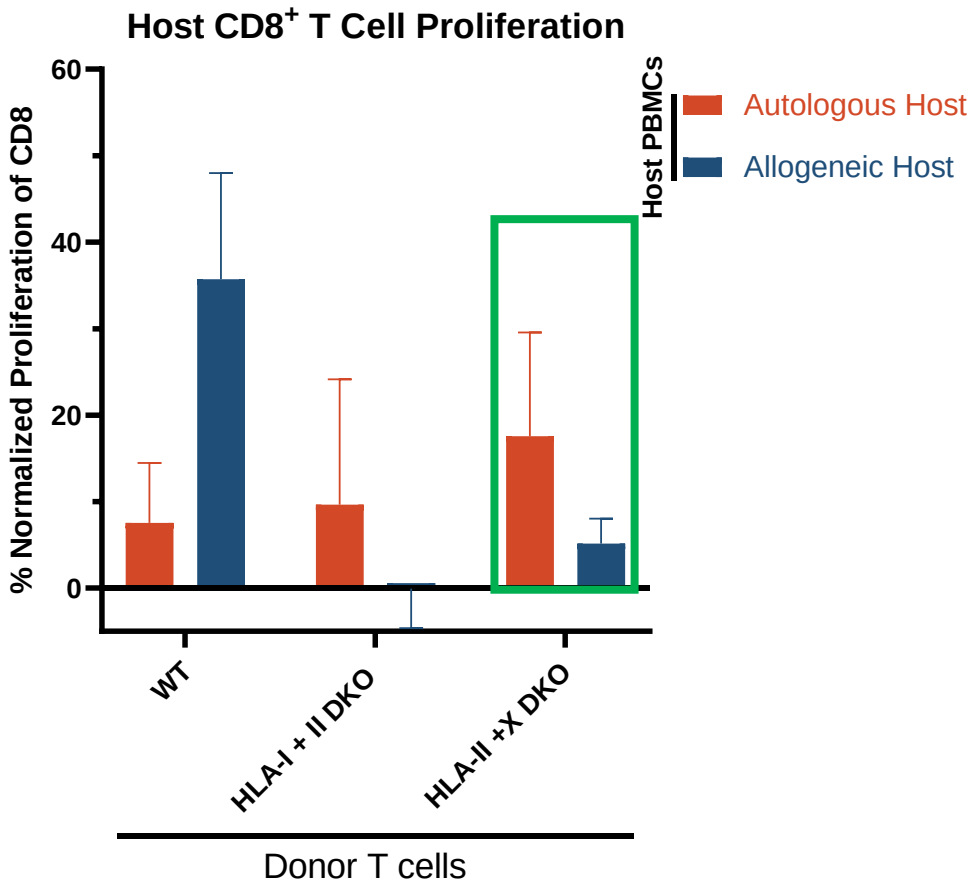
2 Allo T Cells Do Not Elicit Host CD4 or CD8 T Cell Responses

Mixed Lymphocyte Reaction (MLR) Assay



Readout: Host T cell proliferation





- Knockout of Receptor X and HLA-II is equally inert as knockout of HLA-I and HLA-II in terms of triggering the activation and proliferation of host CD4+ or CD8+ T cells

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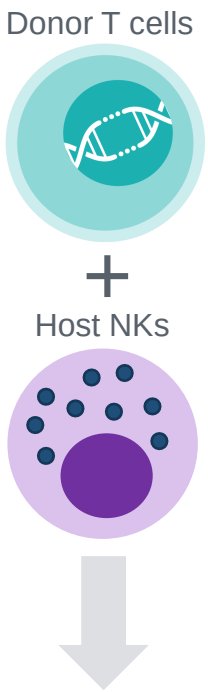
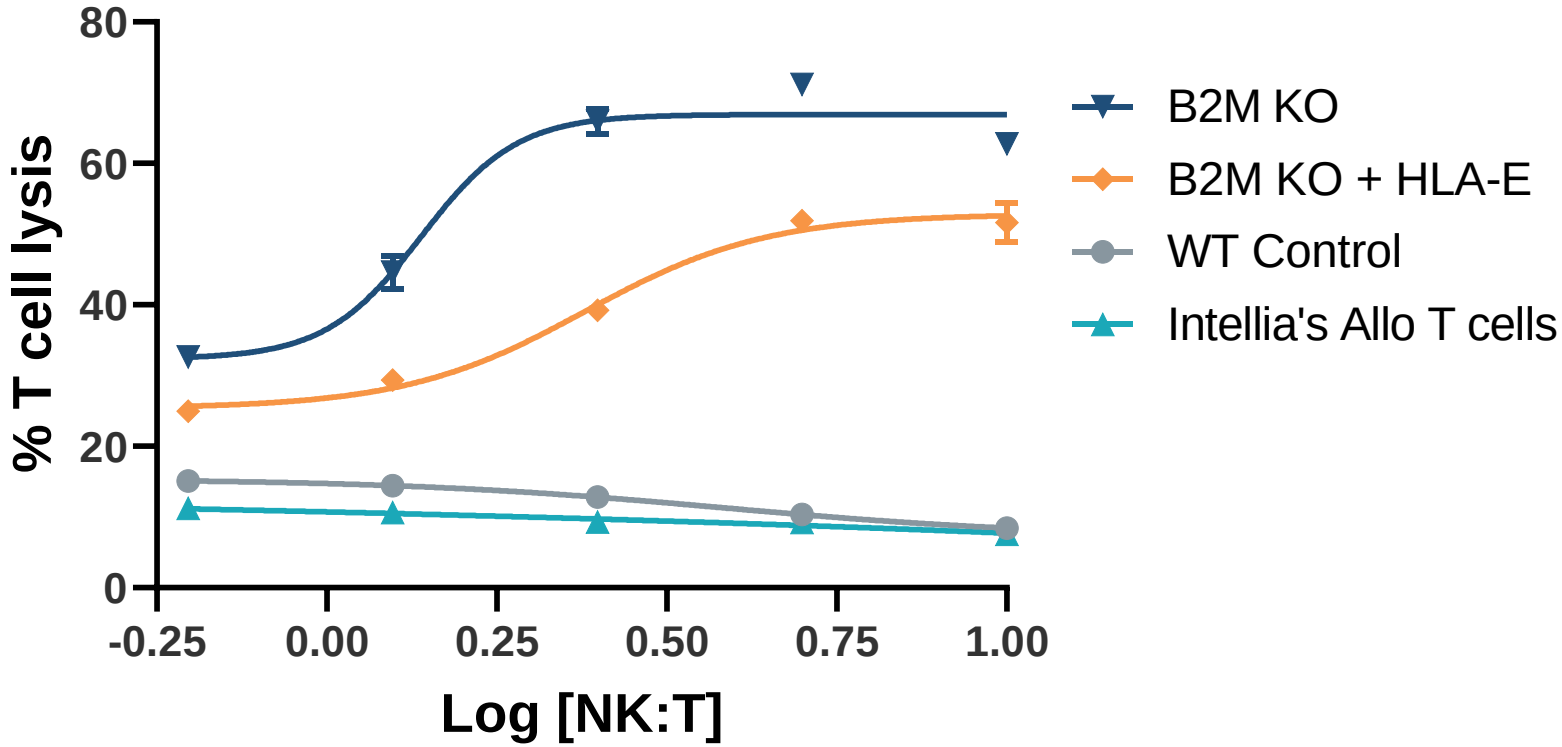
3 Intellia's Allo T Cells are Protected from NK Cell Killing

***In vitro* NK cytotoxicity assay**



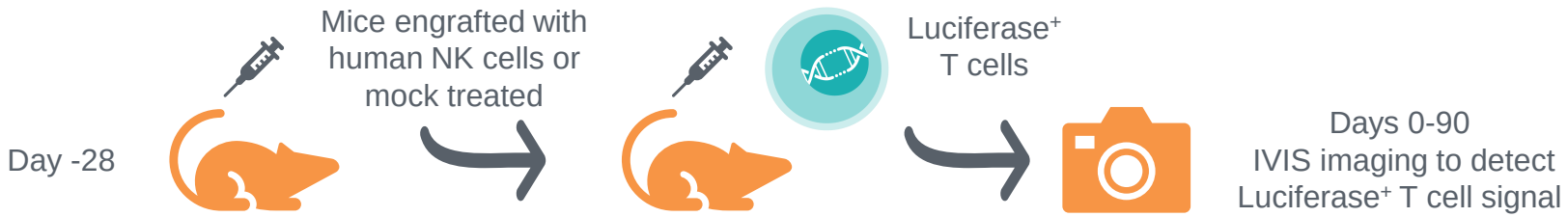
Readout: T cell lysis



- Intellia's Allo T cells are protected from human NK cell elimination
- T cells lacking HLA class I are killed by NK cells; an effect only partially rescued by insertion of HLA-E

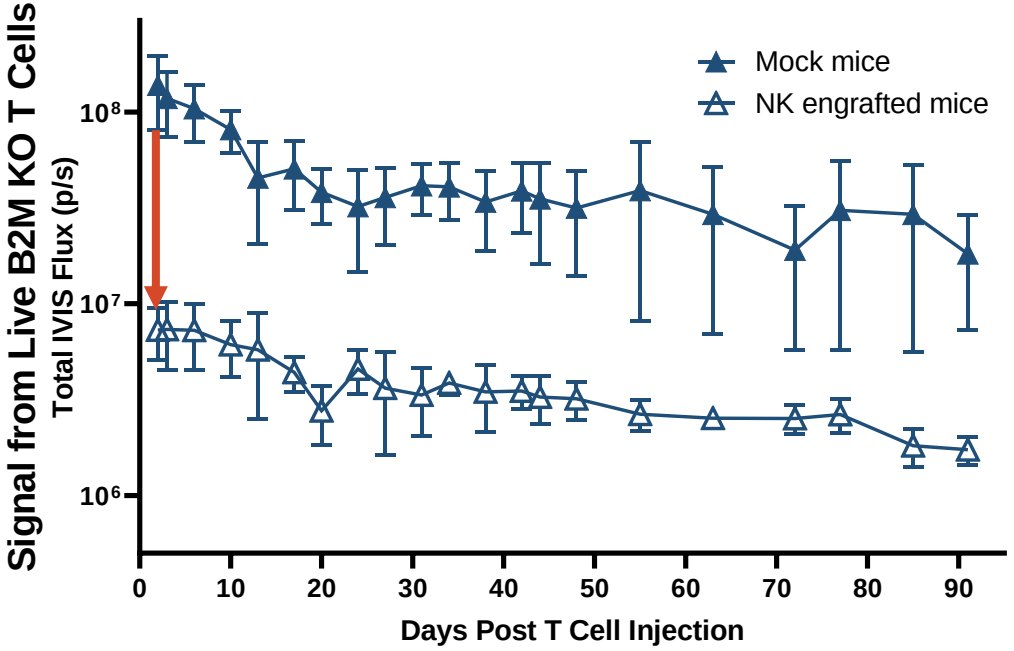
WT Control: Wild-type T cells resistant to NK killing

3 Allo TCR-T Cells Resist NK Cell Killing for at Least 90 Days *In Vivo*



B2M Knockout T cells

>90% B2M KO T cells killed by NKs within 24h



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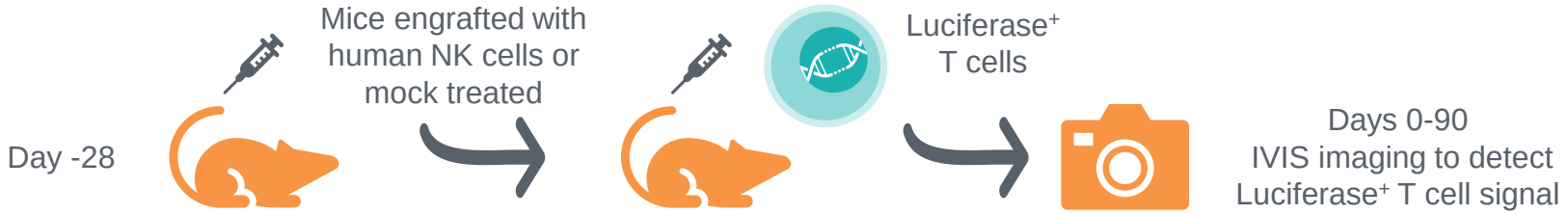
3 Allo TCR-T Cells Resist NK Cell Killing for at Least 90 Days *In Vivo*



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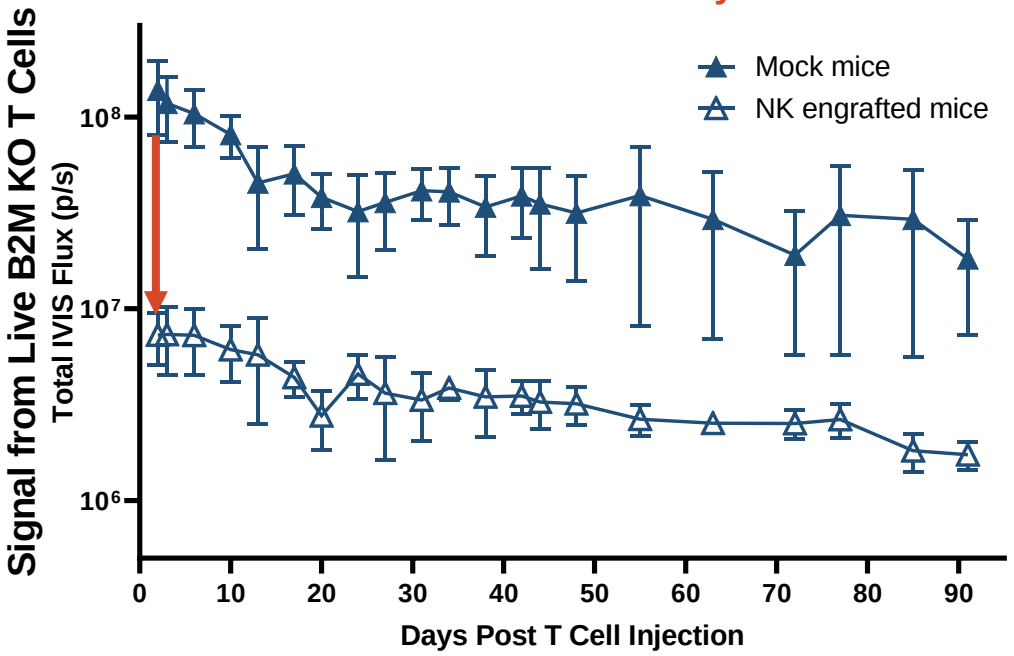
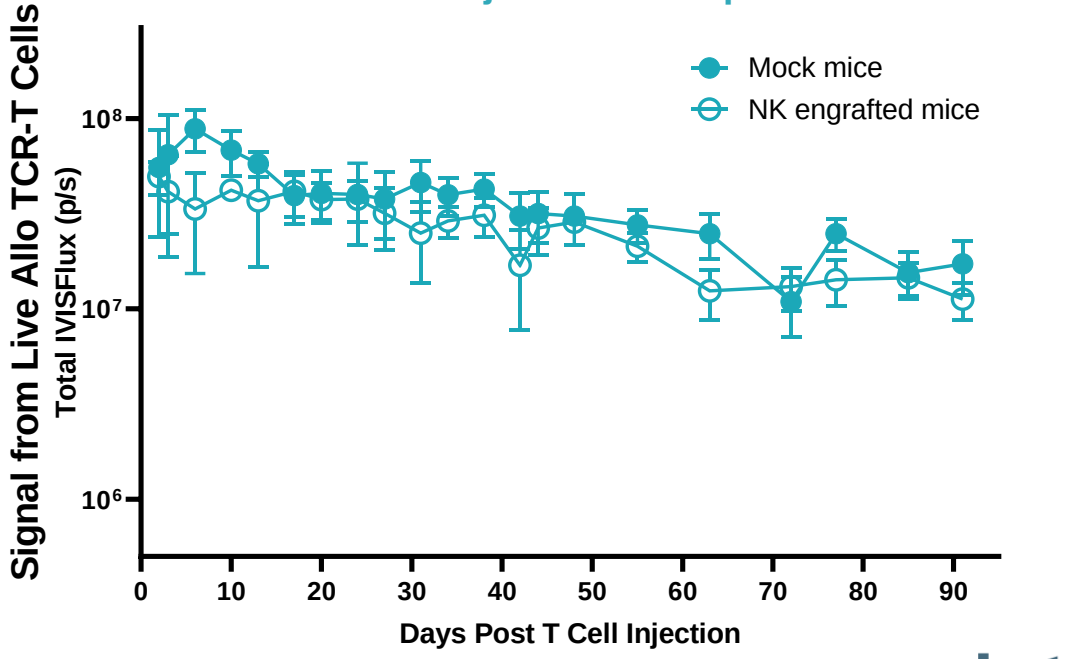


Allo TCR-T Cells

Minimal Allo T cell rejection in the presence of NK cells



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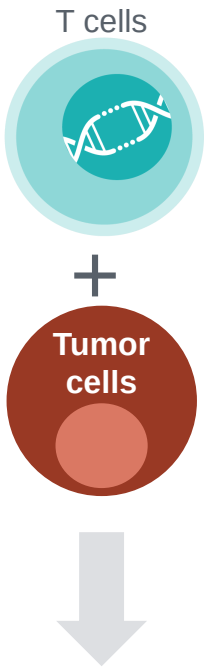
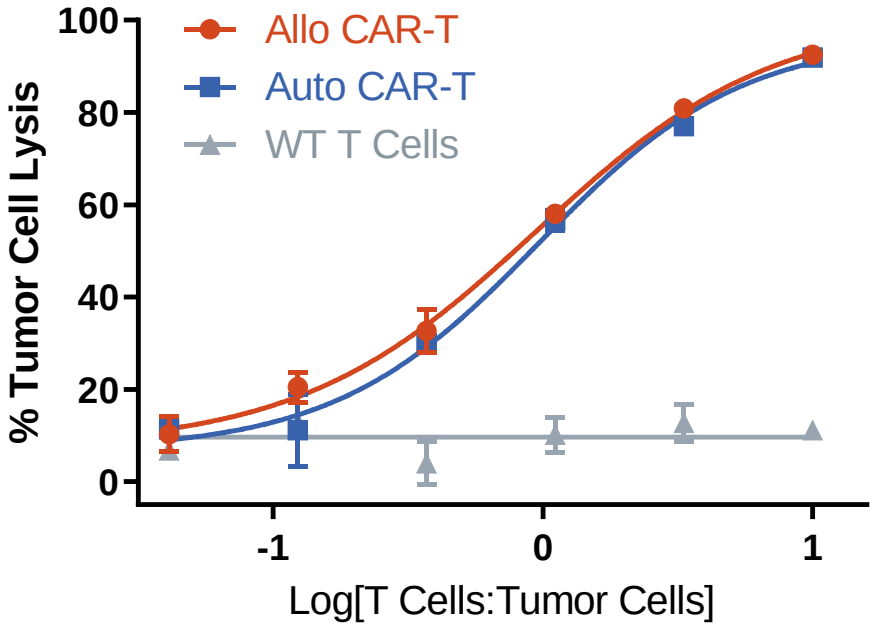
Allo T Cells Have Comparable Tumor Cell Killing Activity to Autologous T Cells

***In vitro* T cell cytotoxicity assay**

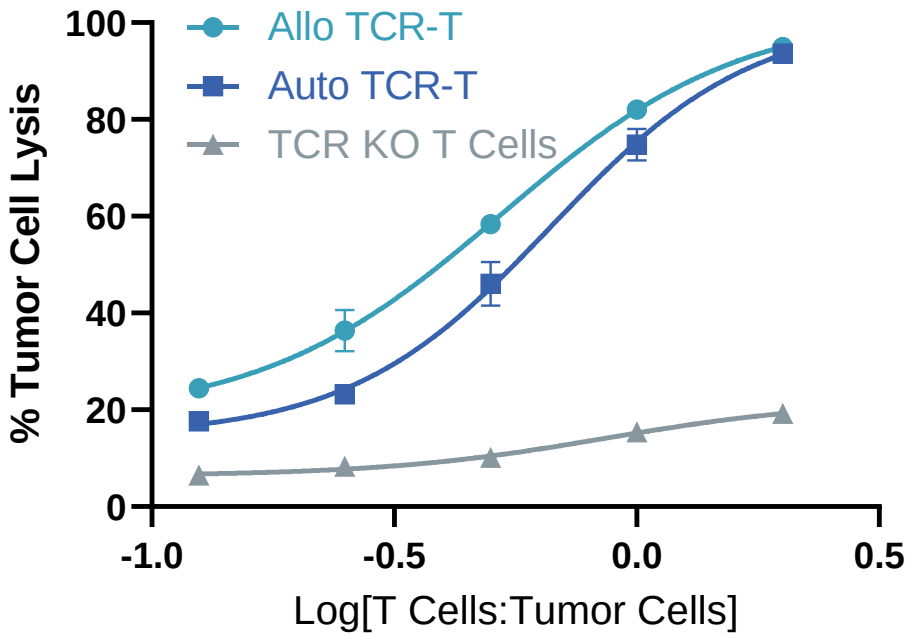


Readout: Tumor cell lysis

Allo CAR-T Cells



Allo TCR-T Cells



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Key Takeaways

- **Intellia has developed a differentiated allogeneic platform**
  - Highly efficient TCR knockout eliminates GvHD issue
  - Allogeneic solution avoids recognition by CD4 and CD8 T cells
  - Allogeneic T cells are protected from NK cell killing *in vitro* and *in vivo*
  - Approach does not depend on immune suppression of the host
- **Allogeneic platform is readily deployable for TCR-T and CAR-T cell therapy**
  - Allo TCR-T and CAR-T cells have comparable anti-tumor activity to autologous counterparts *in vitro*
- **Expect to nominate Intellia's first allogeneic development candidate in 1H 2022**

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Summer 2019

It Takes a Village!

Q + A

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