

Clinical Translation of Pluripotent Cell-Derived Off-the-Shelf Natural Killer Cell Cancer Immunotherapy

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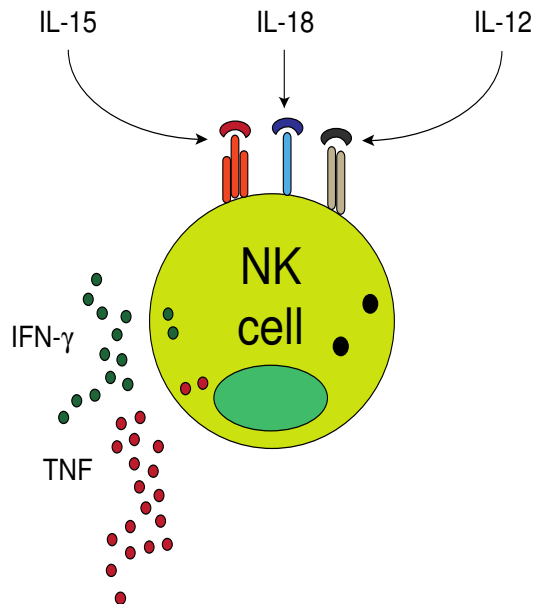
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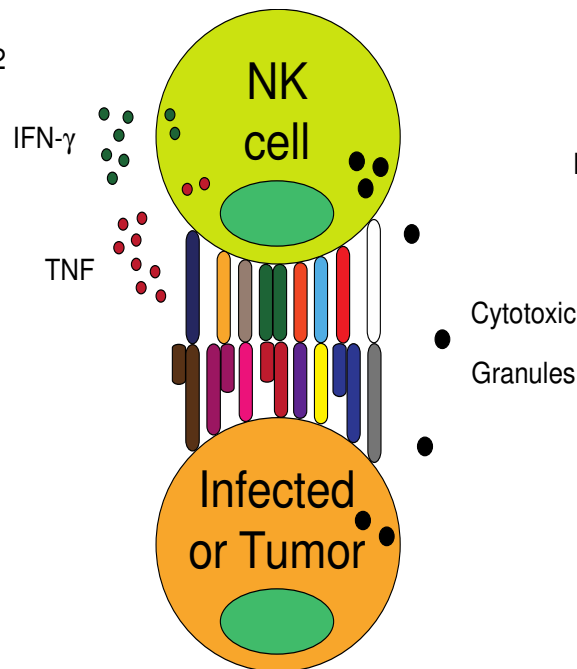


NK Cell Functions in Health and Disease

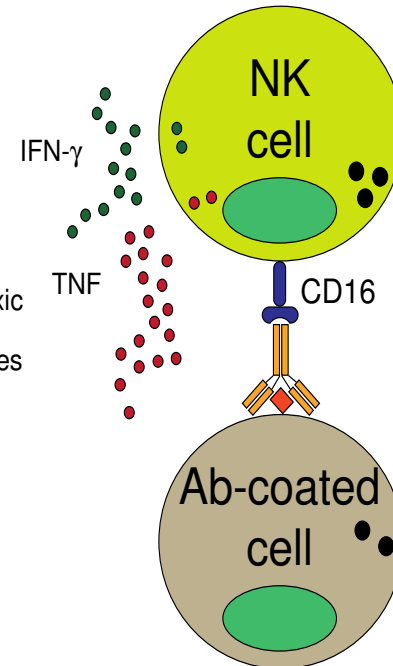
Cytokine Stimulation



Natural Cytotoxicity



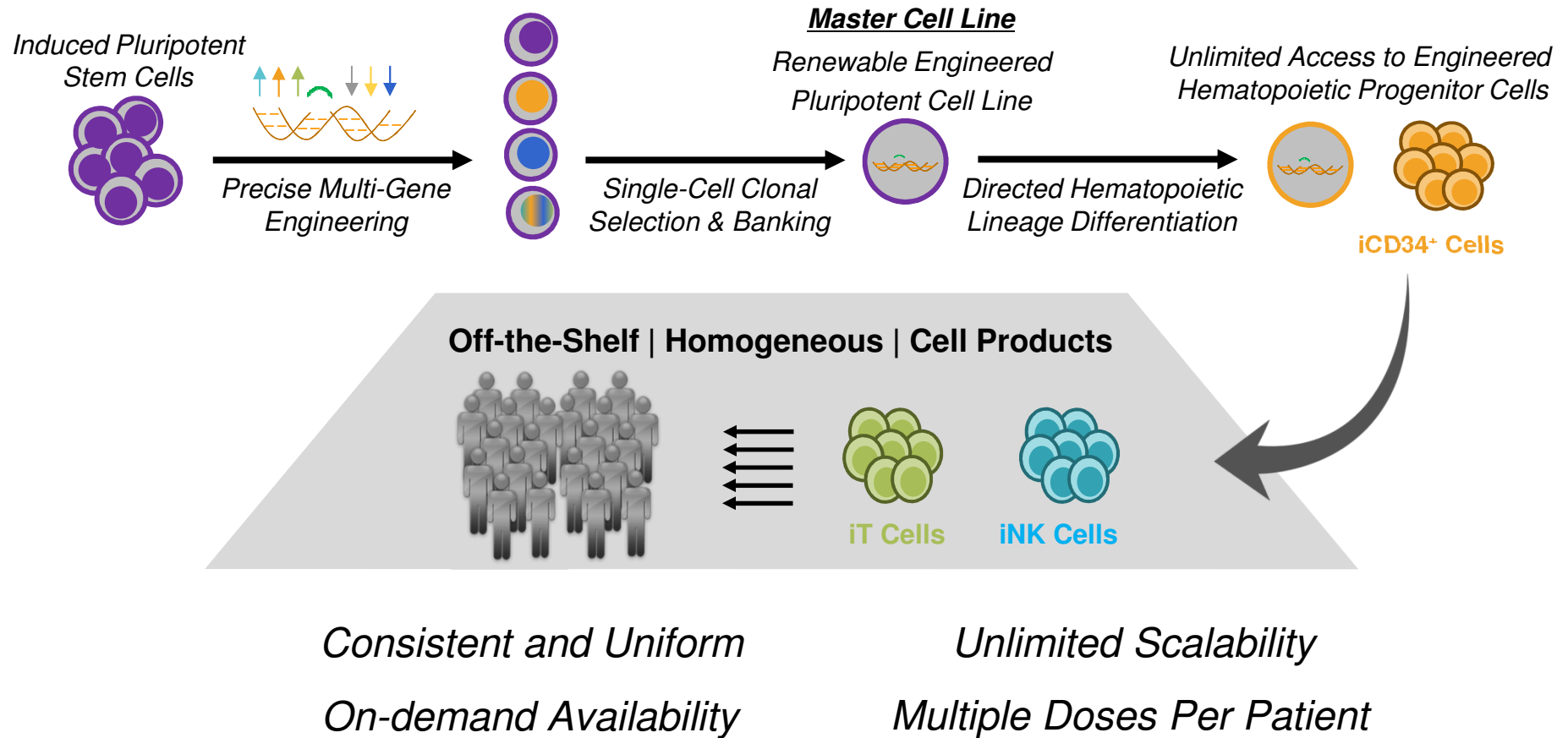
Antibody-Dependent Cellular Cytotoxicity (ADCC)



Limitations to Current NK Cell Therapy

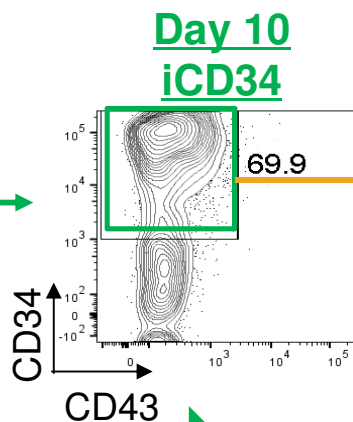
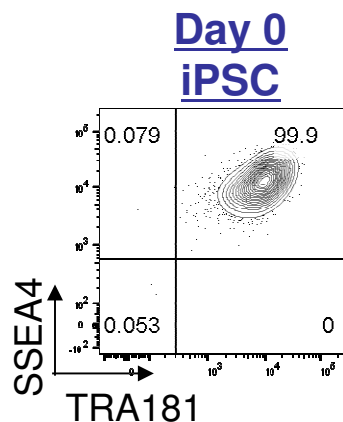
Key Features	Today
Cell Source	Individual Donor into Patient
Genetic Engineering	Random & Variable
Manufacturing	Patient-specific
Product Consistency	Heterogeneous
Delivery	Delayed & Individual Lot Release
Dose-per-Patient	Single
Overall Paradigm	Patient-centric

Off-the-Shelf Hematopoietic Cell Products Derived from Renewable Engineered Pluripotent Cell Lines



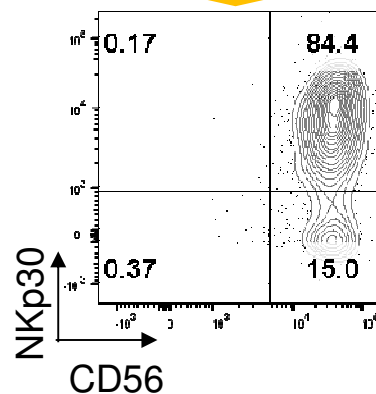
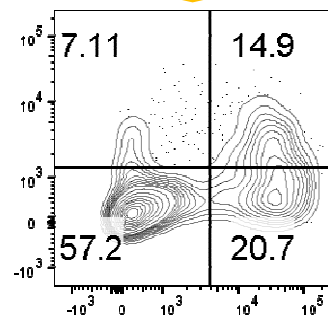
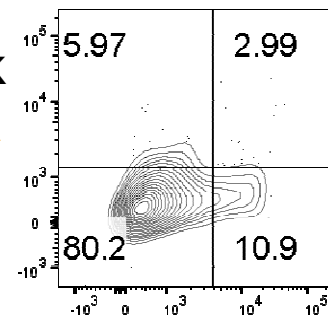
Addresses Critical Limitations of Individual-Patient Cell Therapies

iPSC → iNK Manufacturing Process



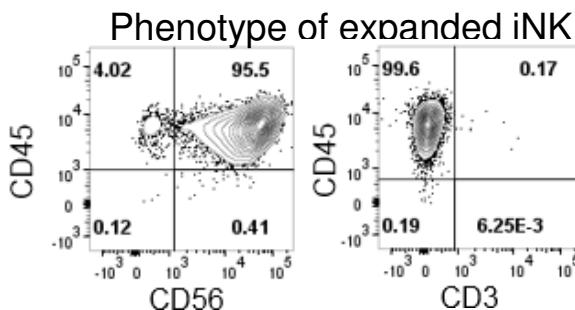
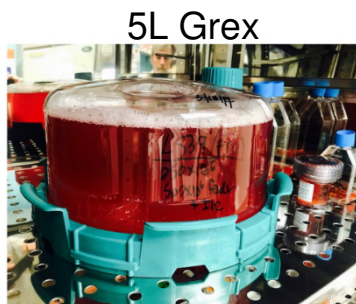
**Initiation of iNK
Commitment**
OP9-DLL4

NK Cell Expansion
IL15+K562/IL21/41BBL

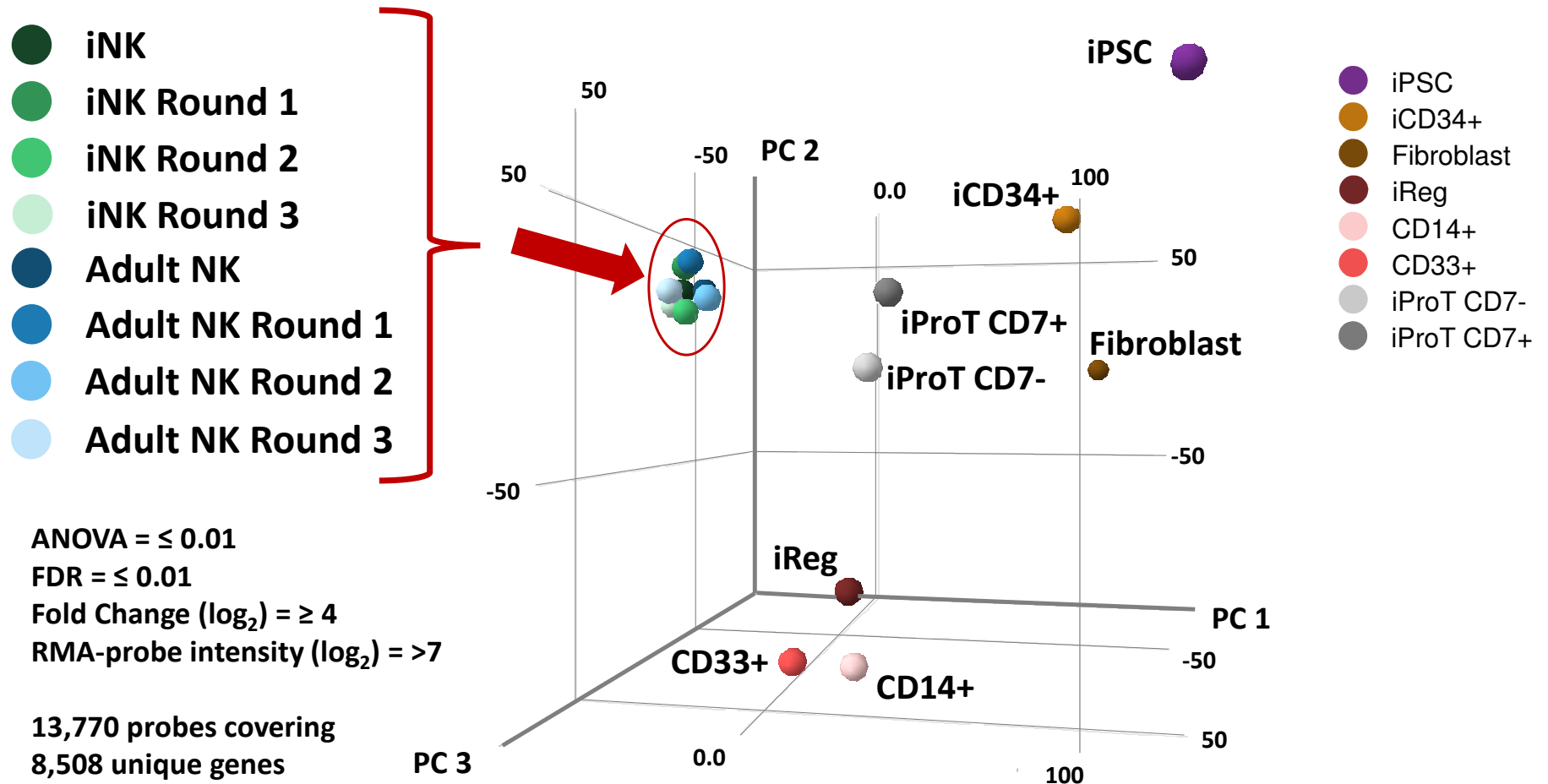


Hematopoietic Differentiation
SCF / BMP4 / VEGF / FLT3L / IL6 / IGF / IL11

✓ 1E6 iPSCs delivers 1E12 NK cells during 44 day manufacturing process (GMP @ UMN)

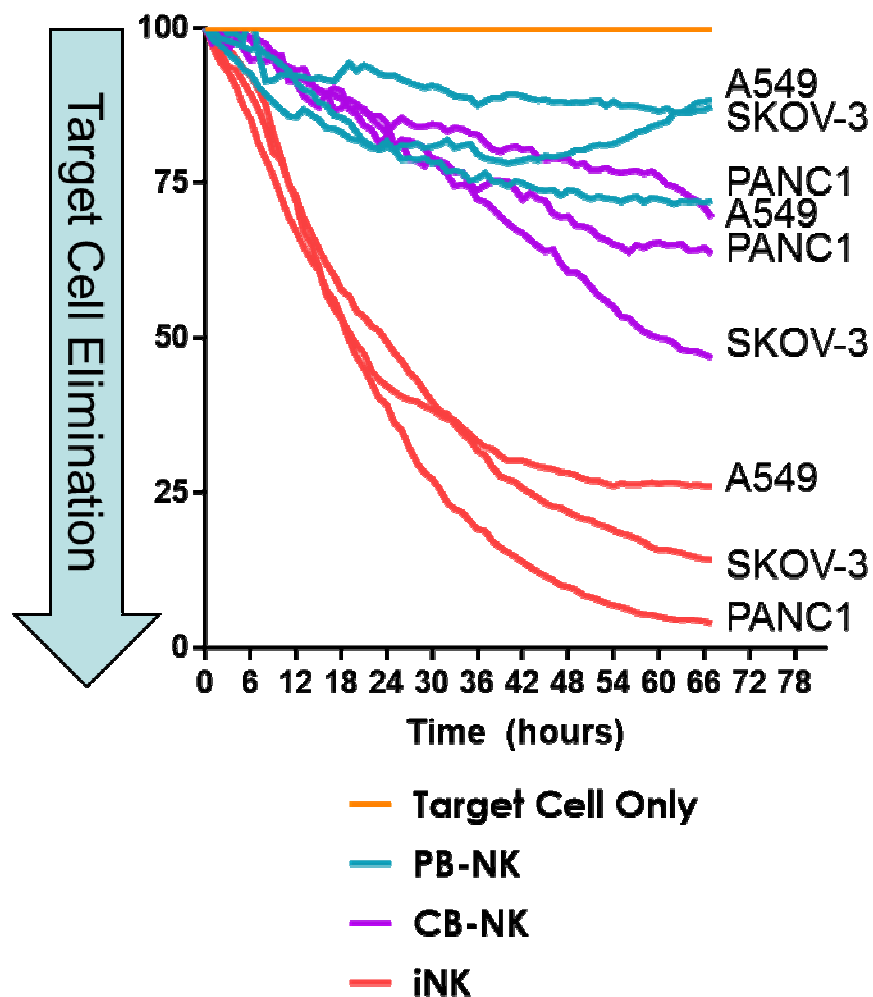


iNK Display Gene Expression Signatures Similar to Expanded Adult PB NK

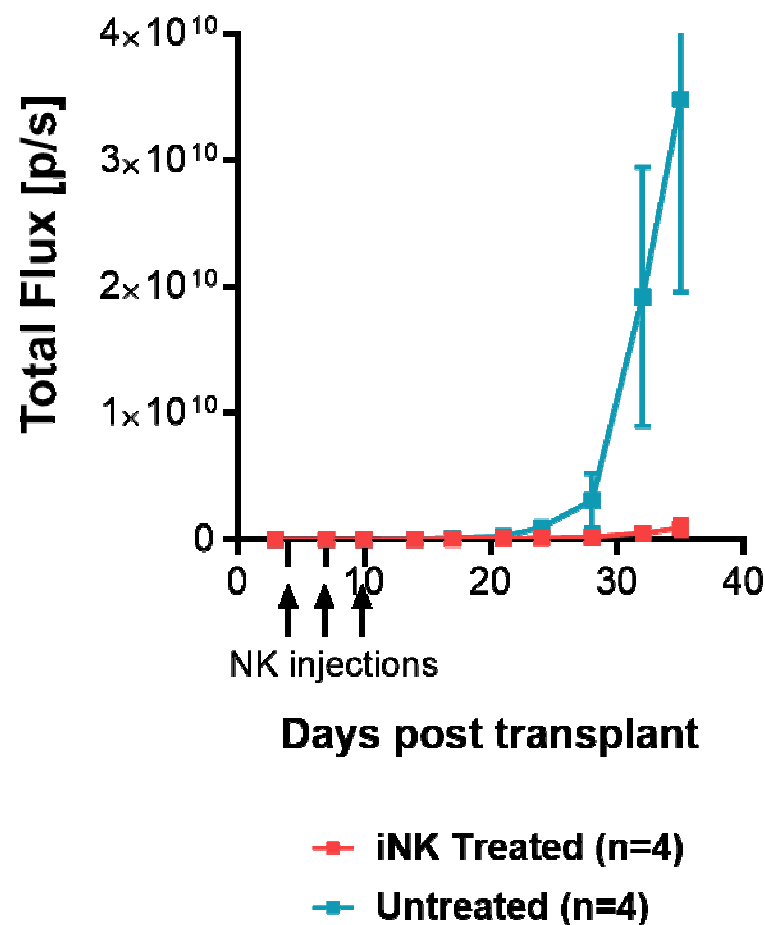


iNK Cytotoxic Function Superior to Expanded Adult PB or UCB NK

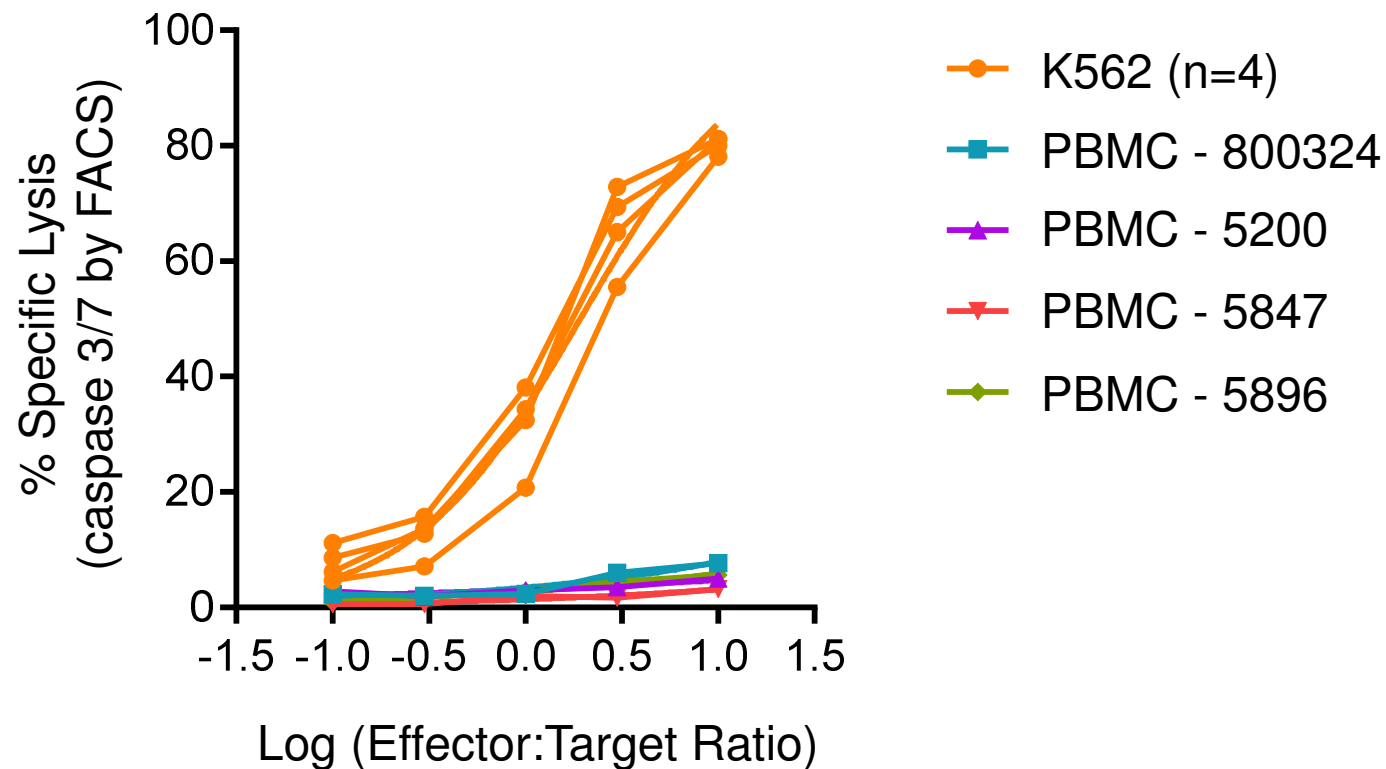
Long-Term Cytotoxicity Assay



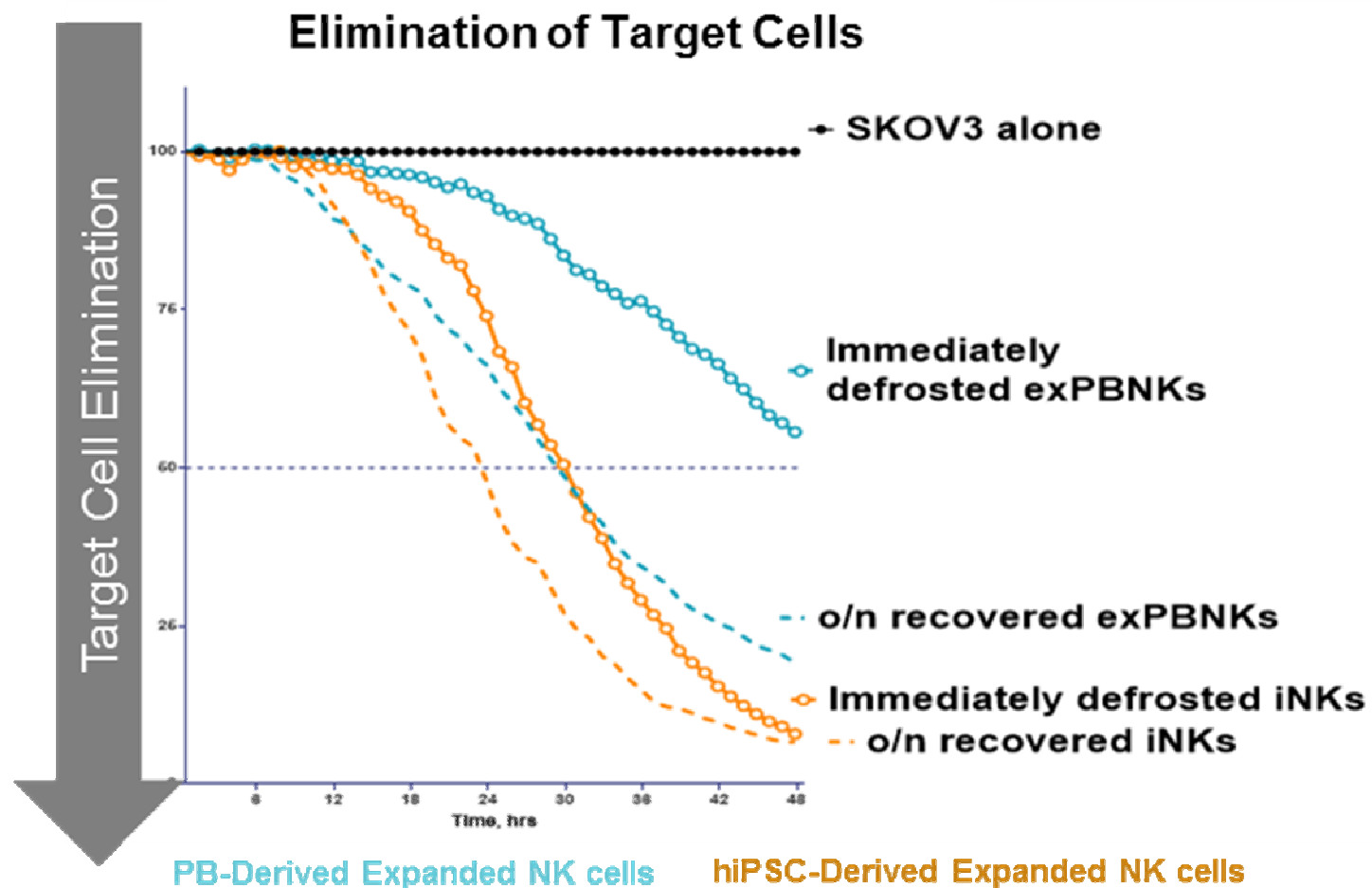
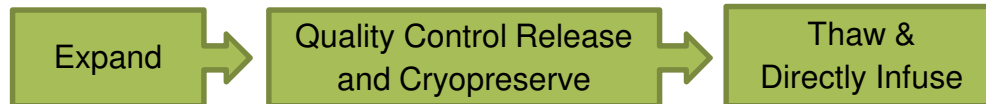
K562 *in vivo* Tumor Model



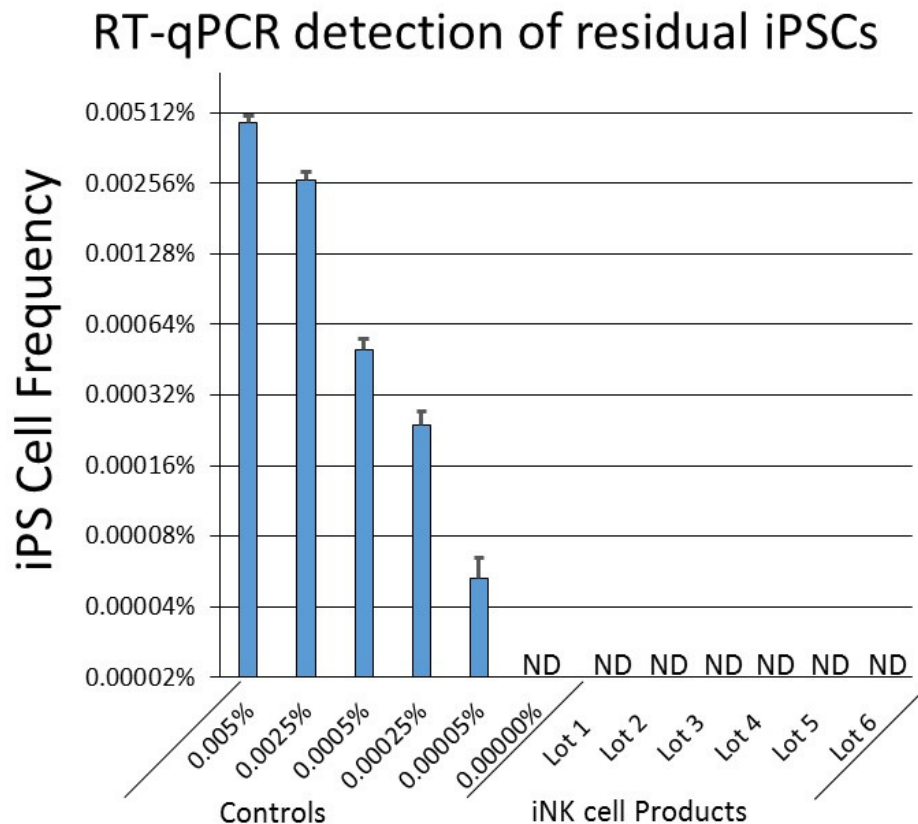
iNK are Highly Cytotoxic to Transformed Cells while Minimally Reactive to Allogeneic PBMCs



Thawed iNK Function Immediately without Overnight Cytokine Exposure



No Residual iPSCs in NK Cell Products



- Determination made analyzing a set of master pluripotency genes (NANOG, OCT4, SOX2, REX1) highly expressed in iPSCs but not in background of NK cells.

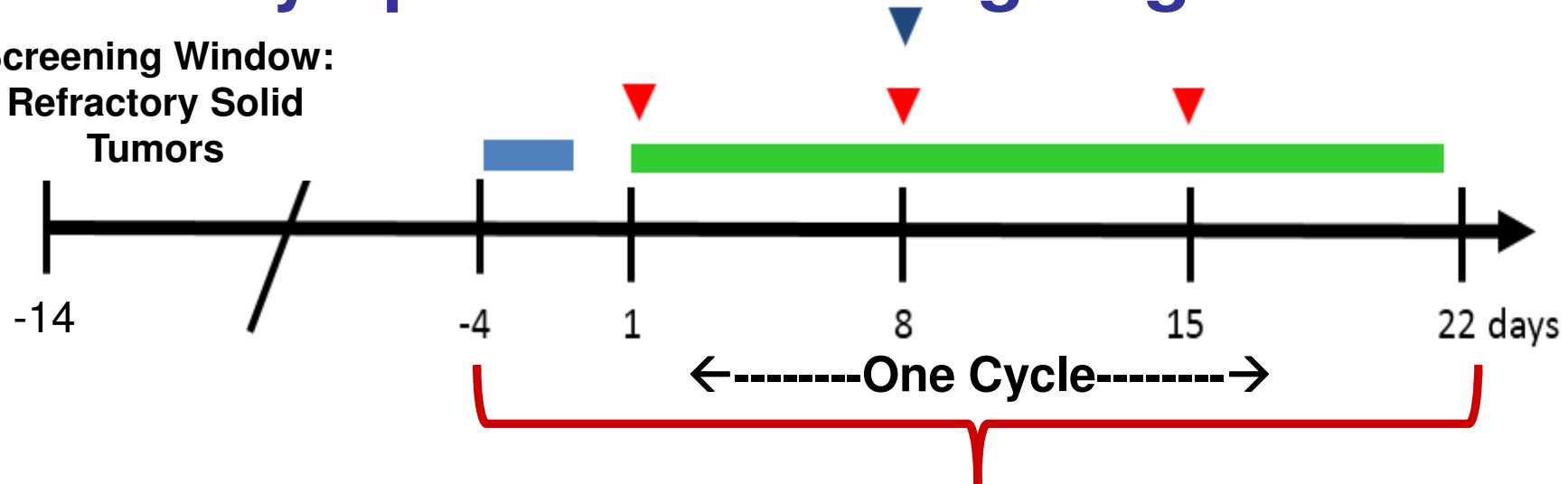
No iPSCs detected at the resolution of 1 in 2 million during multiple iNK cell manufacturing runs

FT500: Regulatory Pathway to Clinical Trials

- FT500 is a first-of-kind off-the-shelf NK cell therapy derived from a renewable source:
 - Multiple Dosing/Scalable
 - Produces cytokines and chemokines with potential to activate tumor beds
 - Can synergize with checkpoint blockade therapy to reduce tumor burden
- Pre-IND and subsequent FDA correspondence has aligned approach to:
 - Safety testing program
 - Manufacturing plan
 - Quality control measures
- Technology transfer to UMN's cGMP facility is complete and IND-enabling manufacturing has commenced
- IND Filing Q1 2018 with first-in-human dosing anticipated mid-2018

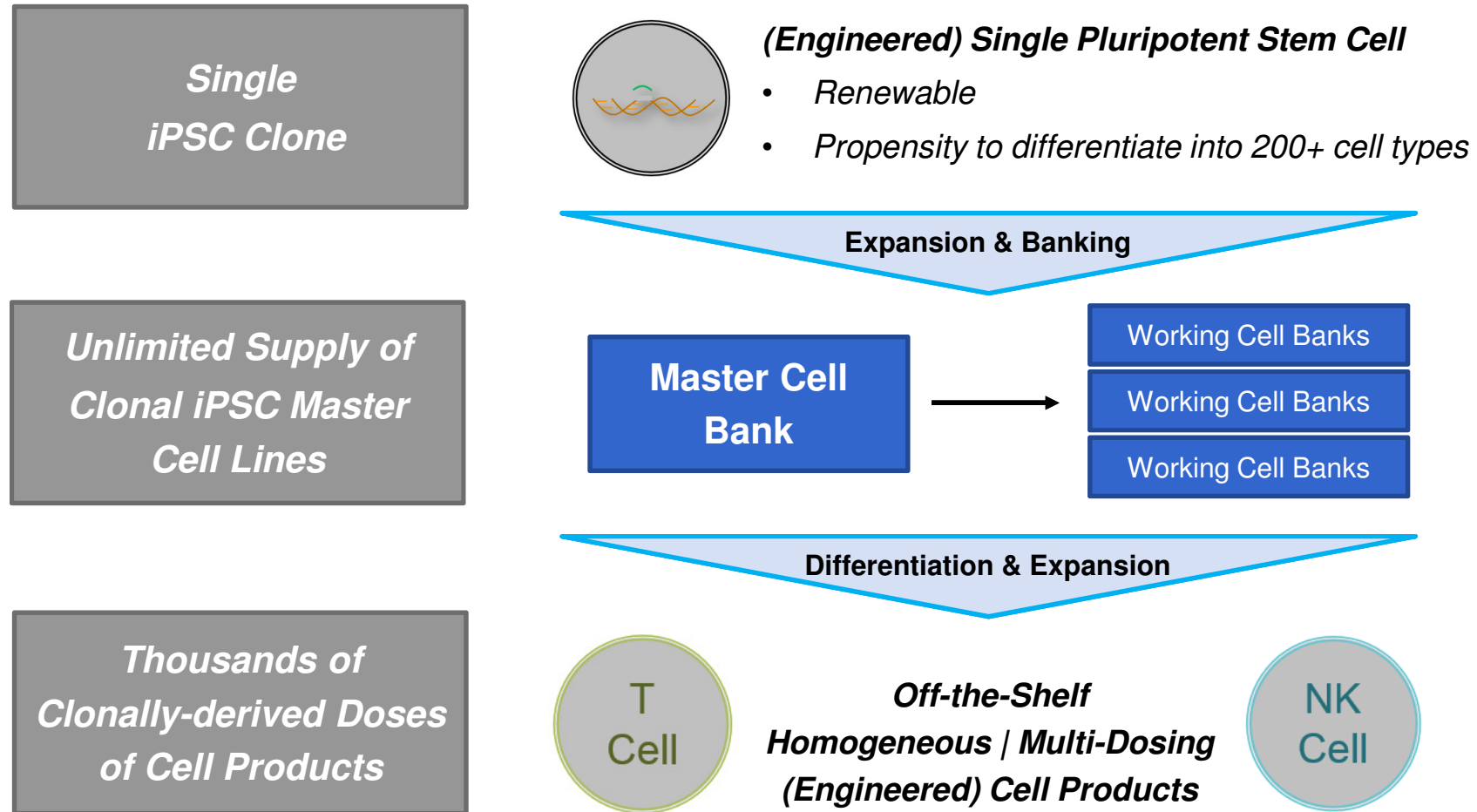
FT500 Clinical Trial Schema: Multiple Cycles of FT500 + Checkpoint Inhibitor Dosed Weekly after Outpatient Lympho-Conditioning Regimen

Screening Window:
Refractory Solid
Tumors



- **Conditioning** Cyclophosphamide: 300 mg/m^2 intravenous (IV) on Day-4 (or Day -3)
Fludarabine 25 mg/m^2 IV on Days -4, -3, (or Day -3 and -2)
- **IL2 (2x/week)** IL-2: 3 million units SC twice weekly from Day1 thru Day21
- ▼ **FT500** 3 doses at 1 week intervals*
- ▼ **Checkpoint Inhibitor** Given per SOC dose and frequency until disease progression

iPS-Derived Off-the-Shelf Cell Products Are Clonal With Precision Control Of Function



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