cGMP Mass Production of FT538, a First-of-Kind, Off-the-Shelf, Multiplexed Engineered Natural Killer Cell Cancer Immunotherapy Derived from a Clonal Master Induced Pluripotent Stem Cell Line

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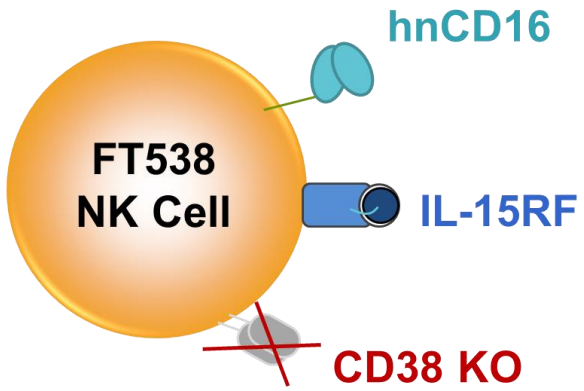
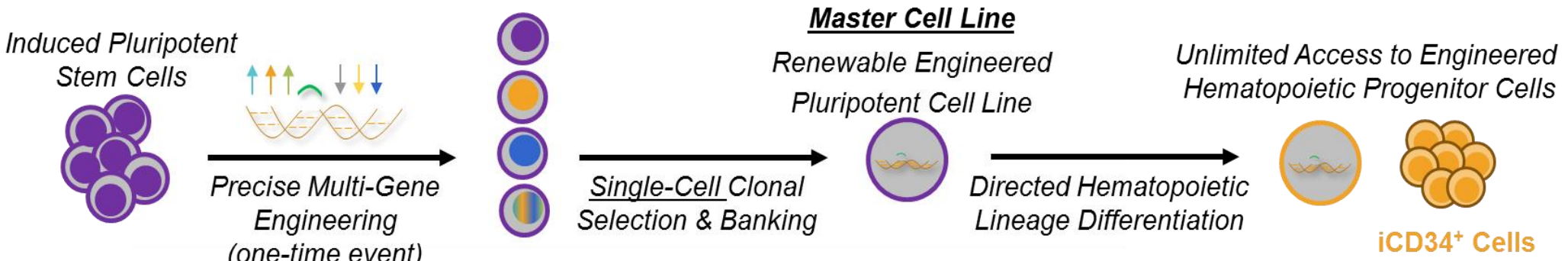
FT538 is an Investigational, Off-the-shelf, Multiplexed Engineered Natural Killer (NK) Cell Cancer Immunotherapy

- FT538 NK cells are derived from a clonal master induced pluripotent stem cell (iPSC) line engineered with three functional components to enhance innate immunity:
  1. A high-affinity 158V, non-cleavable CD16 Fc receptor (hnCD16) modified to augment ADCC activity.
  2. An IL-15 receptor fusion protein (IL-15RF) which promotes survival and persistence and reduces dependency for exogenous cytokine support.
  3. Deletion of CD38 to eliminate anti-CD38 antibody mediated NK cell fratricide.

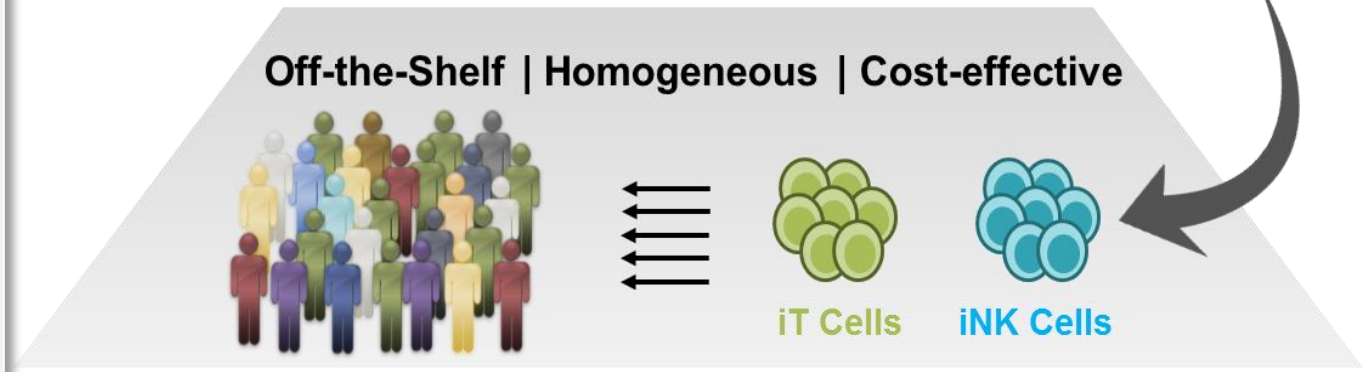


Use of a Clonal Master Engineered iPSC Line as a Starting Cell Source Enables Routine Mass cGMP Production & Supports Off-the-Shelf Availability



Cleared INDs Under Clinical Investigation

- **FT500** (Off-the-shelf) combined with CPB therapy to overcome resistance
- **FT516** (Off-the-shelf Engineered NK cells) genetically edited to enhance antibody-directed cellular cytotoxicity
- **FT596** (Off-the-shelf Multi-Factor Engineered NK cells) genetically edited to target multiple tumor antigens
- **FT538** (Off-the-shelf Multi-Factor Engineered NK cells) genetically edited to enhance persistence and for use with daratumumab
- **FT819** (Off-the-shelf TCR-less TRAC-CAR T cells) genetically edited to elicit a durable response in lymphoma and leukemia



Does not require patient-sourced cells

Eliminates stochastic editing variability associated with pool engineering

Consistent, reliable and cost-effective product forms

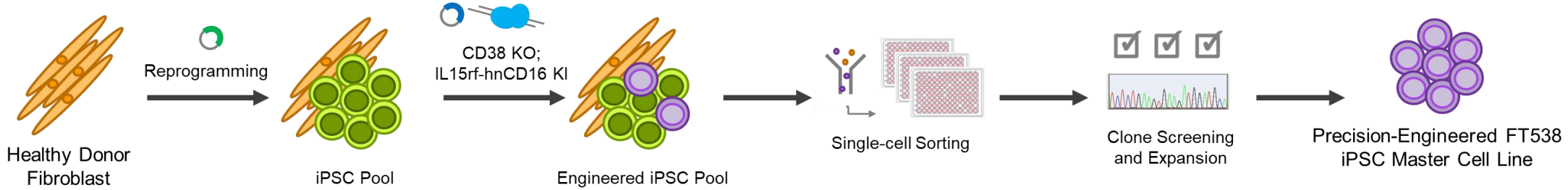
Unprecedented scalability

Off-the-shelf production of cells

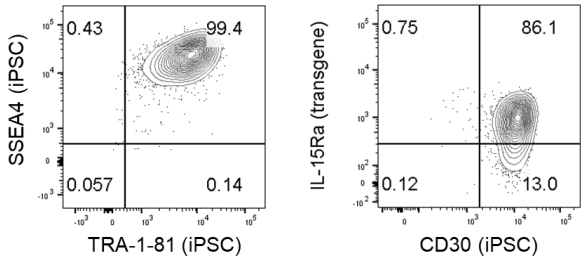
Addresses Critical Limitations of Patient- and Donor-Sourced Cellular Therapies

Generation of FT538 Fibroblast-derived Clonal iPSC Line Engineered with Multiple Modalities to Enhance NK Cell Functions and Persistence

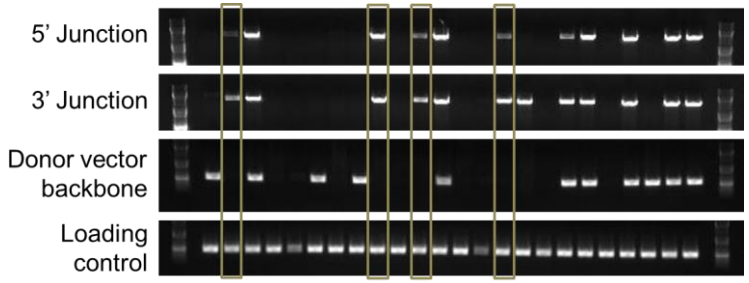
A **Workflow for Generation of FT538 Engineered Fibroblast-Derived iPSC Master Cell Line**



B **Engineered iPSC Clone Phenotype Post-Sort**



C **PCR Analyses of CD38-targeted IL15RF-hnCD16 iPSC Clones**



D **Engineered FT538 iPSC Maintains Genomic Stability**

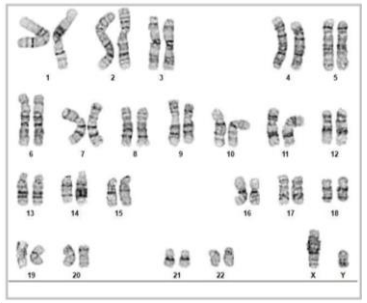


Figure 1

A. Workflow for the generation of FT538 engineered fibroblast-derived iPSC MCBs. The engineering strategy resulted in: CD38 knockout, expression of an IL-15 receptor alpha fusion (IL-15RF) protein, and expression of a high-affinity non-cleavable CD16 (hnCD16)

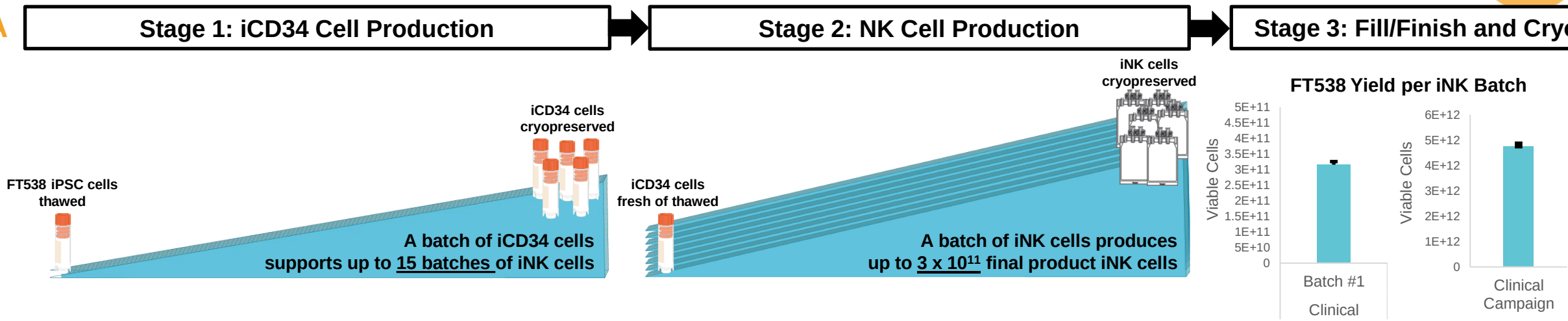
B. Flow cytometry profiles of reprogrammed and engineered clonal iPSC clone are depicted.

C. PCR assays to screen for clones with specific cassette integration into the *CD38* locus with no random integration are displayed

D. Characterization of the genomic stability of FT538 iPSC MCB was performed and results are displayed.

Routine cGMP Production of FT538 Consists of 3 Stages

A



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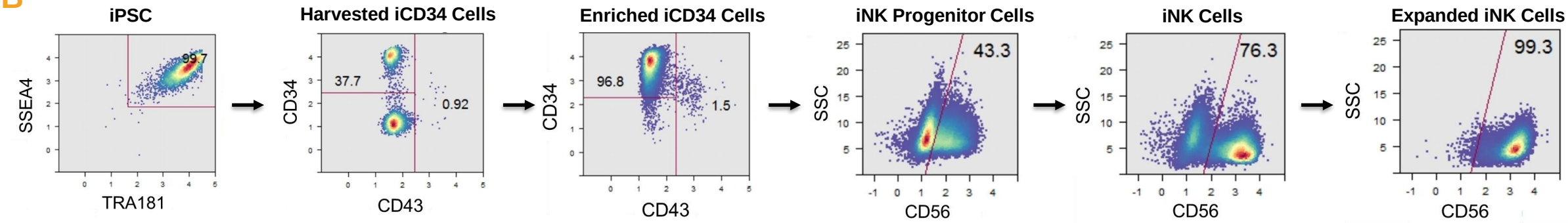


Figure 2

A. The clonal master engineered iPSC line serves as a renewable source for the routine cGMP mass production of FT538 drug product. Routine cGMP manufacture of FT538 drug product consists of three stages: Stage 1: Differentiation of the clonal master engineered FT538 iPSC line to iPSC-derived CD34-expressing (iCD34) hematopoietic progenitor cells, Stage 2: Further differentiation to and expansion of NK cells from either fresh or cryopreserved iCD34 cells, and Stage 3: Fill/finish and cryopreservation of the FT538 drug product. The yield of viable FT538 cells for the clinical batch was 3.1 x 10^{11} viable cells. The cGMP clinical manufacturing campaign was filled into over 300 units of cryopreserved drug product. Based on the number of CD34-derived batches that could be produced from the initial iPSC thaw (15 batches), the cGMP campaign had a theoretical yield of 4.5 x 10^{12} FT538 NK cells.

B. Representative flow cytometry plots of each process step are depicted, from iPSC to final product.

Stage 1: iCD34 Cell Production
FT538 Development & Clinical Batch Characterization

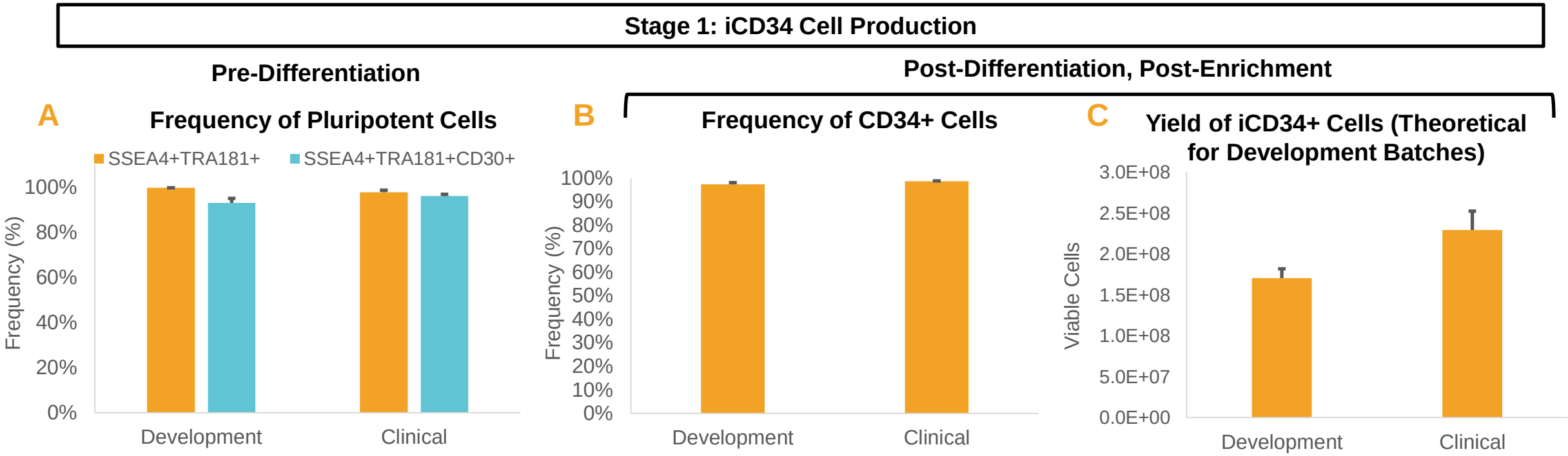


Figure 3

A. Prior to differentiation, the frequency of pluripotent cells was evaluated by flow cytometry. Development batches of FT538 exhibited an average of 100 ± 0.1% SSEA4+TRA181+ and 93 ± 2% SSEA4+TRA181+CD30+ (n=2). Clinical batches exhibited an average of 98 ± 0.8% SSEA4+TRA181+ and 96 ± 0.8% SSEA4+TRA181+CD30+ (n=2).

B. After differentiation to iCD34 cells and enrichment for CD34-expressing cells, frequency of CD34 expression was evaluated by flow cytometry. Development batches of FT538 exhibited an average of 97 ± 0.8% CD34+ (n=2). Clinical batches exhibited an average of 99 ± 0.2% CD34+ (n=2).

C. The theoretical yield of iCD34 cells for development batches was calculated by multiplying the actual yield by the proportional scale factor intended for use in a clinical batch. The theoretical development batch yield ranged from 1.6-1.8 x 10^8 viable cells and the actual yield for the clinical batches ranged from 2.1-2.5 x 10^8 viable cells. The cGMP clinical manufacturing campaign yielded sufficient CD34-expressing hematopoietic progenitor cells to support >15 batches of NK cell differentiation, derived from cryopreserved iCD34 cells.

Stage 2: NK Cell Production
FT538 Development & Clinical Batch Characterization

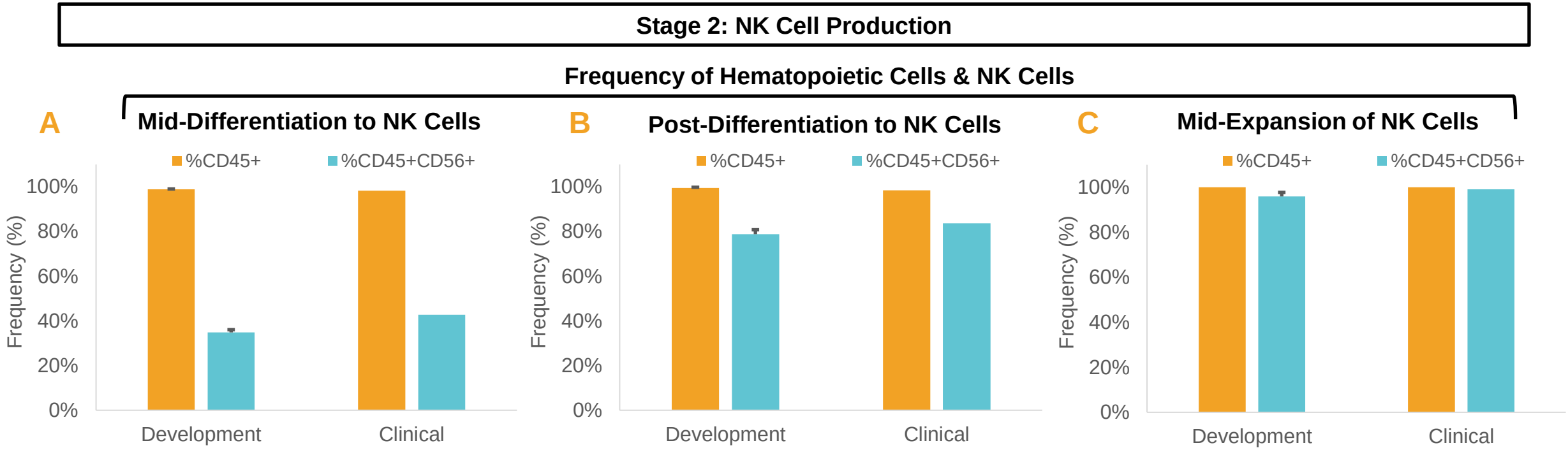


Figure 4

At several processing points during Stage 2: NK Cell Production, cells were evaluated for differentiation to hematopoietic (CD45+) and NK cells (CD45+CD56+).

A. Mid-differentiation to NK cells, development batches exhibited 99 ± 0.2% CD45+ and 35 ± 1% CD45+CD56+ (n=2). The clinical batch exhibited 98% CD45+ and 43% CD45+CD56+ (n=1).

B. Post-differentiation to NK cells, development batches exhibited 99 ± 0.4% CD45+ and 79 ± 2% CD45+CD56+ (n=2). The clinical batch exhibited 98% CD45+ and 84% CD45+CD56+ (n=1).

C. Mid-expansion of NK cells, development batches exhibited 100 ± 0.1% CD45+ and 96 ± 2% CD45+CD56+ (n=2). The clinical batch exhibited 100% CD45+ and 99% CD45+CD56+ (n=1).

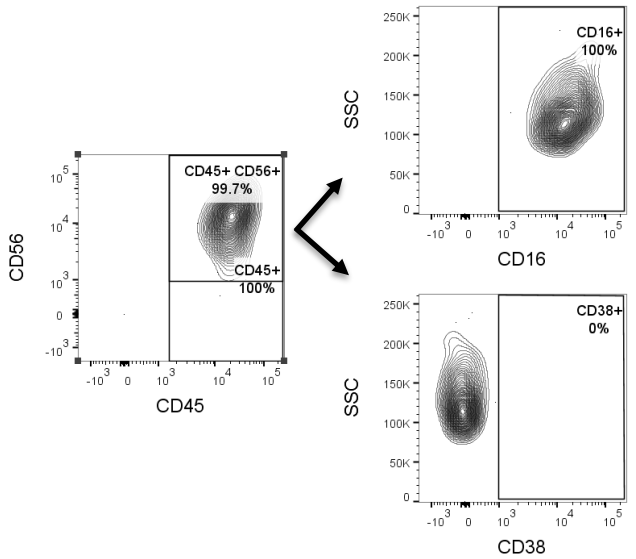
Stage 3: Drug Product Fill/Finish and Cryopreservation
FT538 Development & Clinical Batch Characterization

Stage 3: Drug Product Fill/Finish and Cryopreservation

A FT538 Phenotype and Impurity Characterization Summary

	Development		Clinical
	Batch 1	**Batch 2**	**Batch 1**
CD45+	99%	100%	100%
CD45+CD56+	99%	99%	99%
CD16+	100%	100%	100%
CD38+	0%	0%	0%
Residual iPSC	Not detected	Not detected	Not detected

B FT538 Example Flow Cytometry Plots



C FT538 IFNγ Release in Response to RPMI-8226

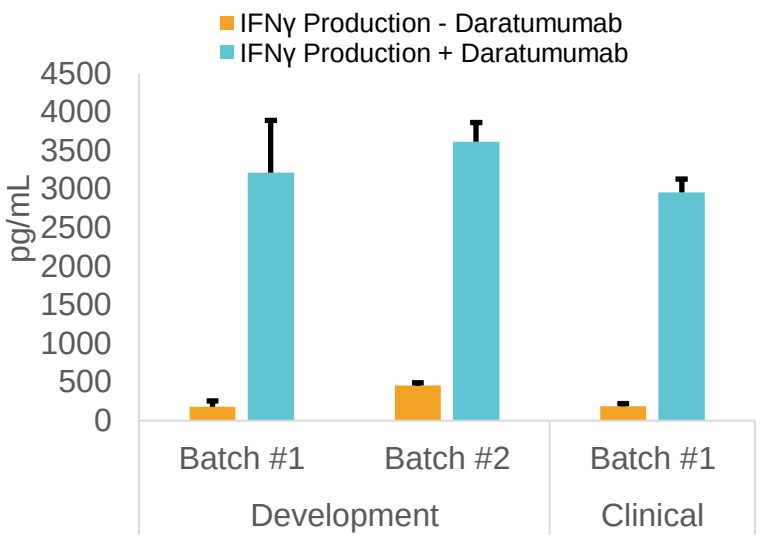


Figure 5

A. FT538 cells were thawed and evaluated for frequency of CD45+, CD45+CD56+, CD16+, and CD38+ by flow cytometry and evaluated for residual iPSC by qPCR. Average results for development and clinical batches are depicted in the table above.

B. Representative flow plots of the final product are displayed for CD45+ and CD45+CD56+ of viable cells, CD16 of CD45+CD56+ viable cells, and CD38+ of CD45+CD56+ viable cells.

C. FT538 cells were thawed and potency was evaluated by measuring IFNγ production in response to RPMI-8226 (CD38+ MM cell line), with and without daratumumab (dara). Development batch #1 released an average of 178 ± 77 pg/mL and 3217 ± 674 pg/mL IFNγ without and with dara, respectively (n=2). Development batch #2 released an average of 454 ± 36 pg/mL and 3613 ± 251 pg/mL IFNγ without and with dara, respectively (n=3). Clinical batch #1 released an average of 184 ± 37 pg/mL and 2956 ± 177 pg/mL IFNγ without and with dara, respectively (n=3).

Summary

- FT538 NK cells are derived from a clonal master induced pluripotent stem cell (iPSC) line engineered with three functional components to enhance innate immunity: a novel hnCD16 Fc receptor; an IL-15RF; and the elimination of CD38 expression.

- A clinical batch of FT538 drug product has been manufactured, which produced a total of 3×10^{11} FT538 NK cells filled into over 300 units of cryopreserved drug product. Based on the number of CD34-derived batches that could be produced from the initial iPSC thaw (15 batches), the cGMP campaign had a theoretical yield of 4.5×10^{12} FT538 NK cells.
  - The clinical batch of FT538 drug product is comprised of uniformly engineered CD56+ NK cells with homogeneous expression of hnCD16 and lacking expression of CD38. Importantly, there were no residual iPSCs detected in the FT538 drug product.
  - Additionally, the FT538 drug product exhibited potent effector function in a candidate potency assay measuring IFN-γ release in response to RPMI-8226 target cells in the presence of daratumumab.

- An Investigational New Drug application for FT538 has been cleared by the U.S. Food and Drug Administration (FDA).
  - Clinical study will be a multi-center, multi-dose Phase I clinical trial for the treatment of patients with relapsed/refractory (r/r) acute myelogenous leukemia (AML) and multiple myeloma (MM).
  - The dose-escalation utilizes a 3+3 design to identify the maximum tolerated dose of three doses of FT538 on Days 1, 8, and 15 as a monotherapy in r/r AML (Regimen A) and in combination with daratumumab (Regimen B) or elotuzumab (Regimen C) in r/r MM.
  - The trial will test up to five FT538 dose levels ranging from 50 million to 1.5 billion cells, and up to 105 patients will be enrolled.