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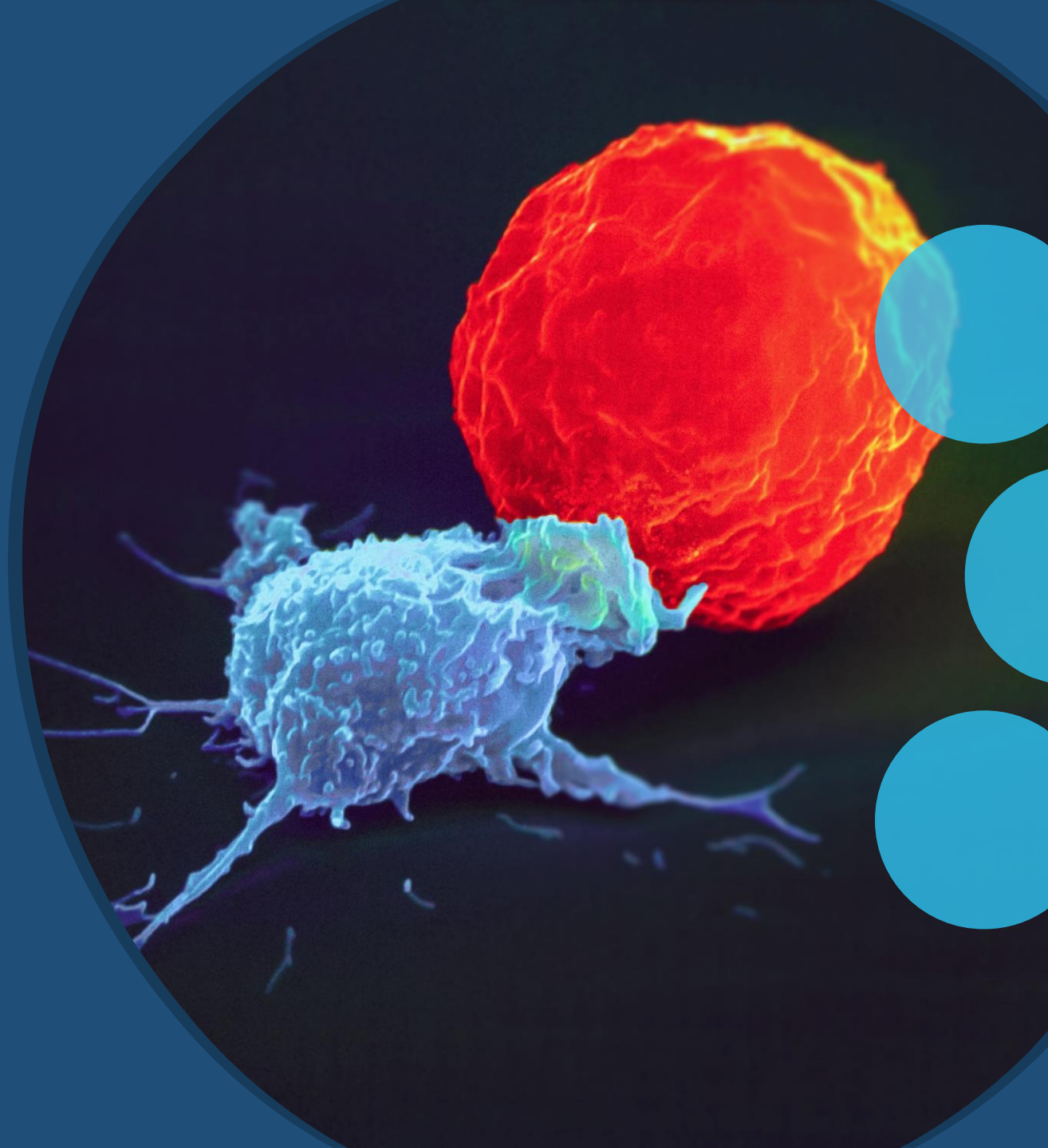
Allogeneic Natural Killer Cells Engineered for Cancer Therapy

B2DG

February 18, 2020



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Outline

- Cell therapies for cancer: progress and limitations
- Nkarta platform
- Lead program
  - NKX101

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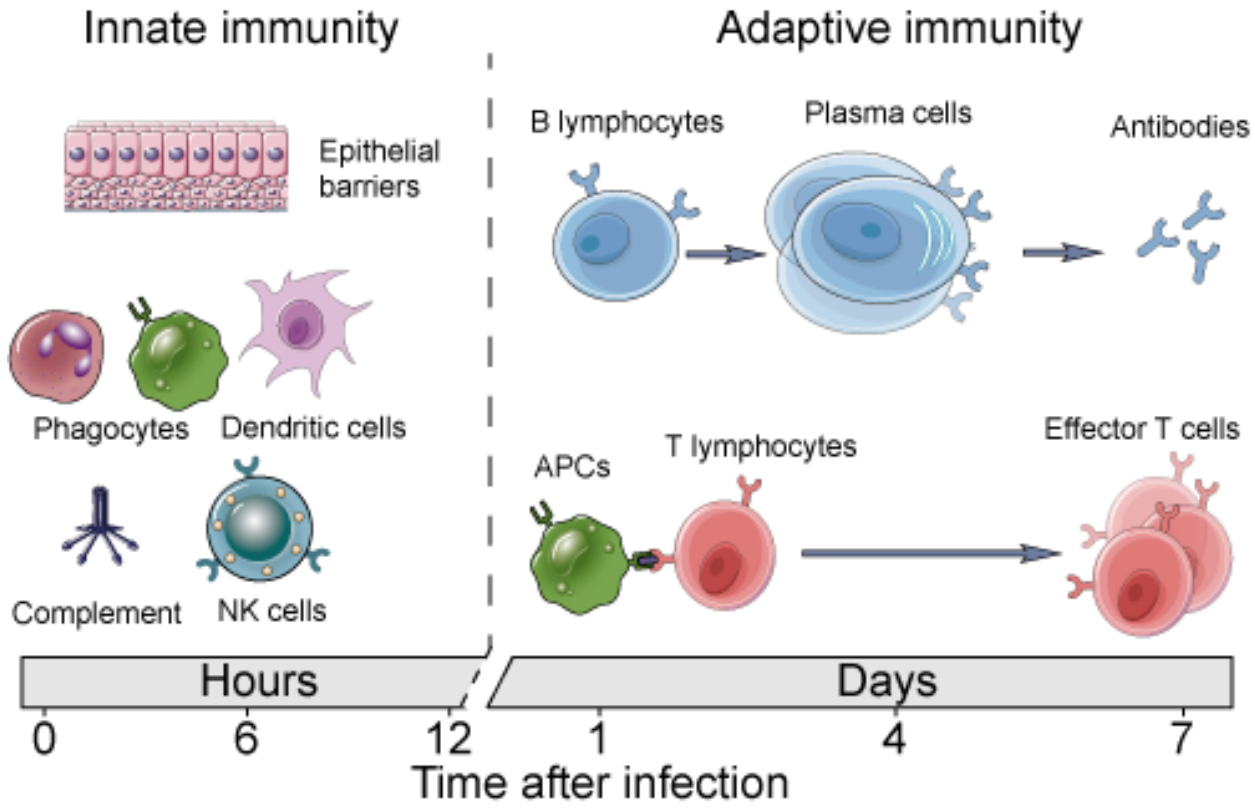
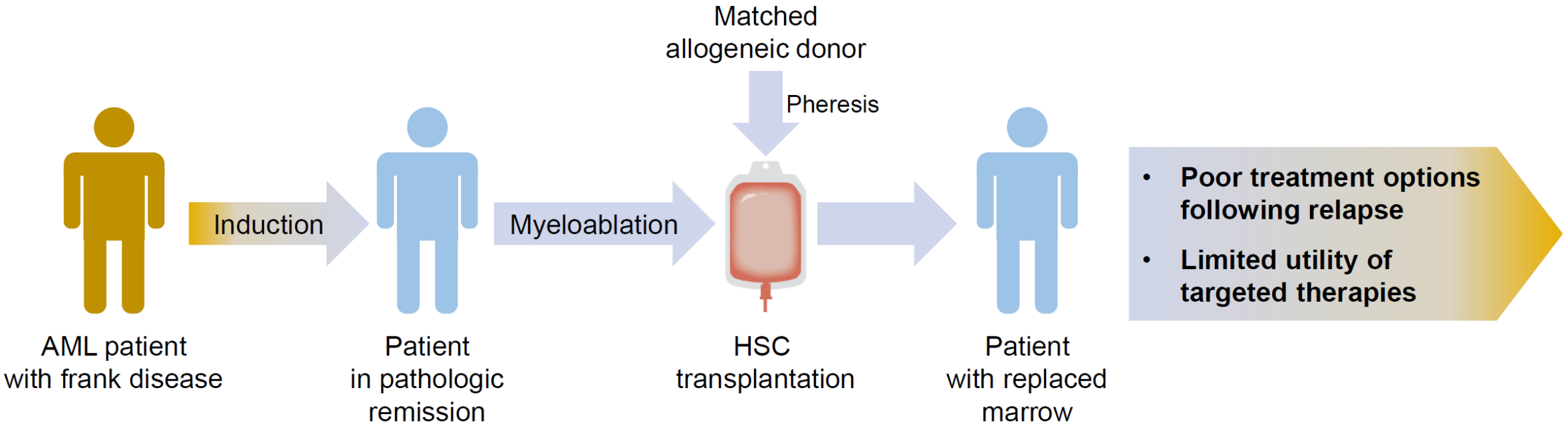
Cell therapies for cancer

Innate and adaptive immune function

- Innate immune cells, including NK cells, act as the first responders of the immune system
- Innate immune cells use pattern recognition
- Adaptive immune responses develop more slowly, but are more specific
- Vaccines and immune checkpoint inhibitors take advantage of adaptive responses



Immune cell therapy for cancer has a long history



Essentially the same product and process since the 1970's

Hematopoietic stem cell transplants can be very effective, but marrow replacement can be harrowing for patients and donors must be very carefully selected for immune (HLA) matching to avoid Graft versus Host Disease (GvHD)

CAR T cells: A new paradigm in cancer therapy

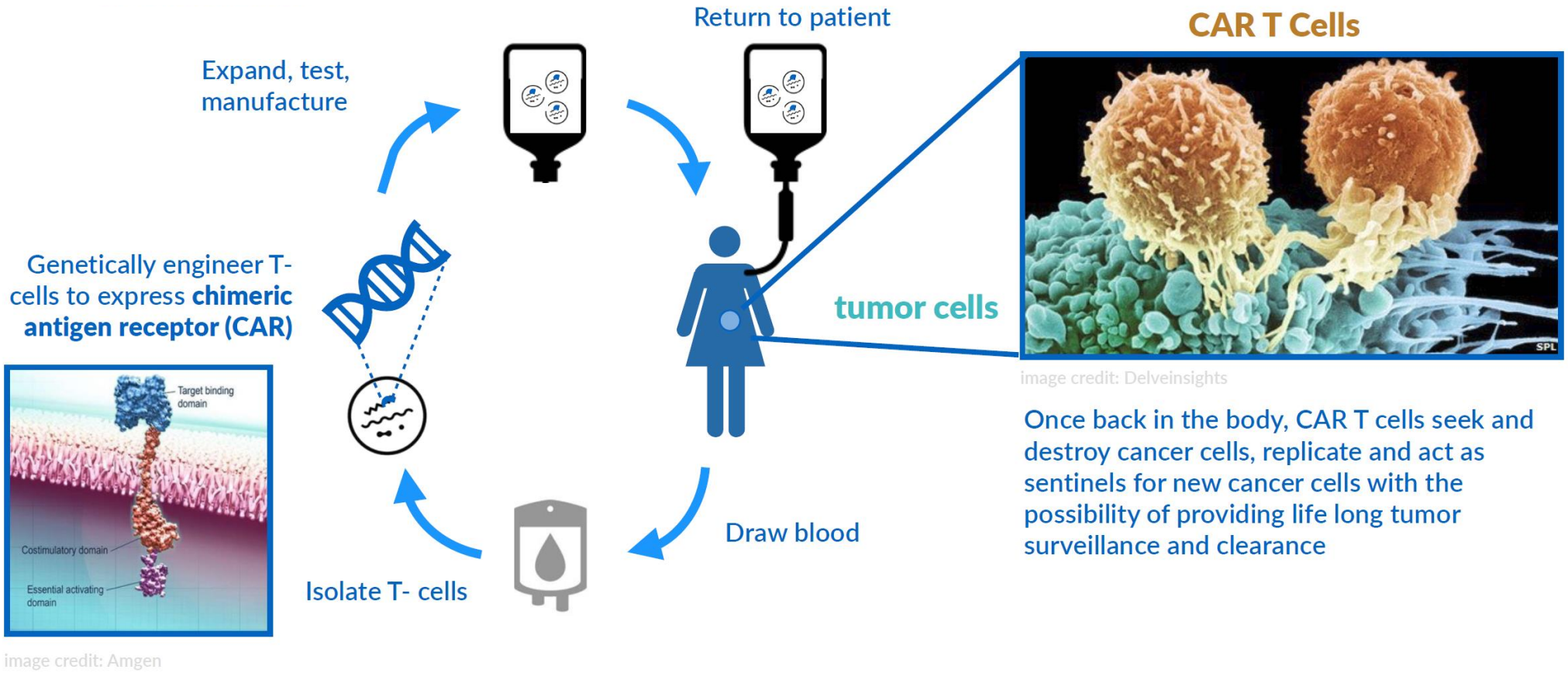


image credit: Amgen

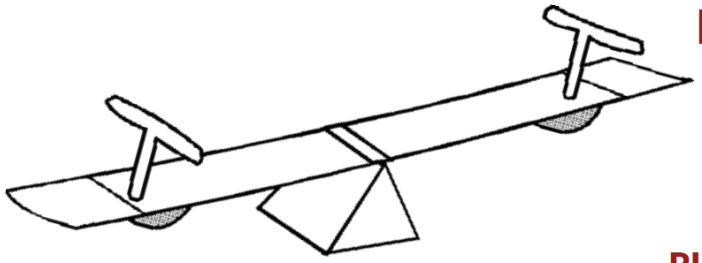
image credit: Delveinsights

Once back in the body, CAR T cells seek and destroy cancer cells, replicate and act as sentinels for new cancer cells with the possibility of providing life long tumor surveillance and clearance

CAR T Cells Chimeric Antigen Receptor T-cells cells are form of engineered immunity; they are designed to bind targets on the surface of tumors and activate a potent immune response against their target

Living cell therapies can have unprecedented potency: but that is sometimes combined with significant toxicity

POTENCY



LIMITATIONS

CURATIVE THERAPY?

Emily Whitehead first pediatric ALL CAR patient: almost 5 years remission

image credit: Emily Whitehead Foundation

6 month overall survival of R/R ALL

STANDARD OF CARE

3-24%

CAR T

78%

RUNAWAY TOXICITY

Runaway cerebral edema cost Juno $1.3B of market cap in one day

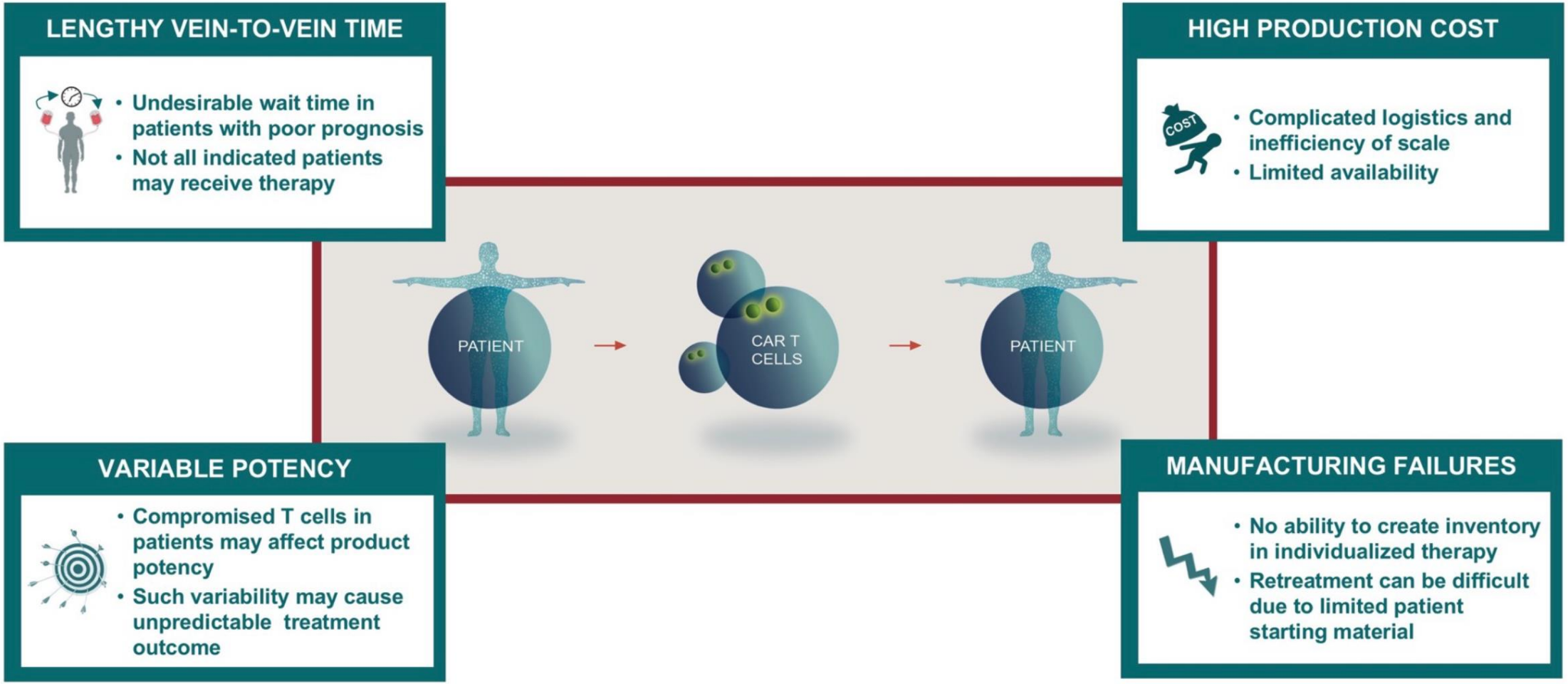
Juno Therapeutics Stops Trial Of Cancer-Killing Cells After 3 Patient Deaths

Three patients have died in a closely watched study of using genetically engineered white blood cells to treat adult leukemia patients, forcing the trial to be put on hold.

LIMITED EFFICACY AGAINST SOLID TUMORS

Kite's clinical trials for CAR T:
KTE-C19 (Zuma 1, Ph1/2)
ALL: CR = 93% (liquid cd19+ tumor)
DLBCL: CR = 47% (solid/liquid CD19+ tumor)

Autologous therapies have limitations that limit adaptation



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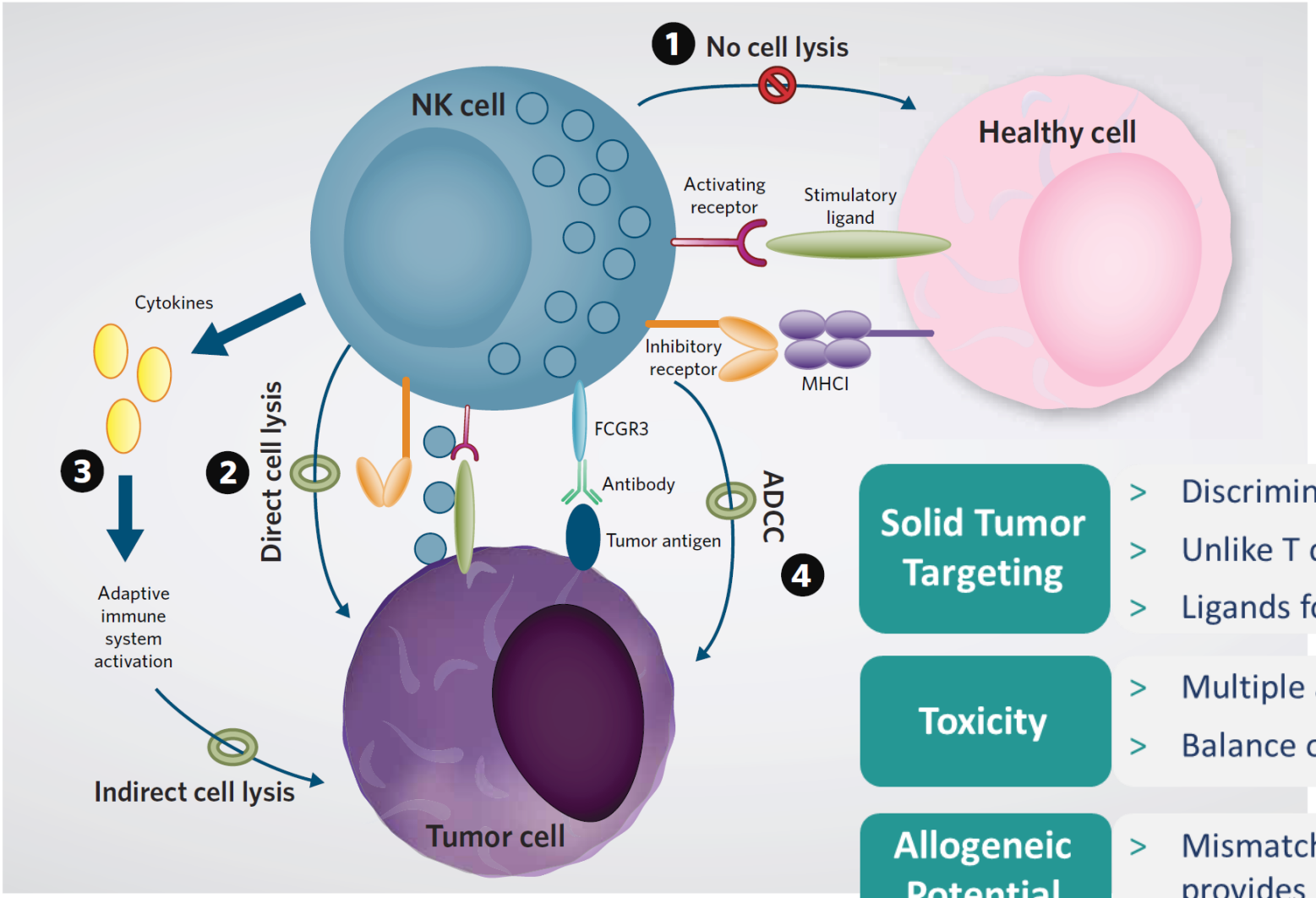
Nkarta Platform

The promise of NK cells for cancer therapy



Solid Tumor Targeting

> Discriminate between healthy and disease cells
> Unlike T cells, do not rely on MHC-I for tumor targeting
> Ligands for NK cell receptors overexpressed in many tumors

Toxicity

> Multiple activating receptors to enhance specificity
> Balance of inhibitory receptors to enhance tunability

Allogeneic Potential

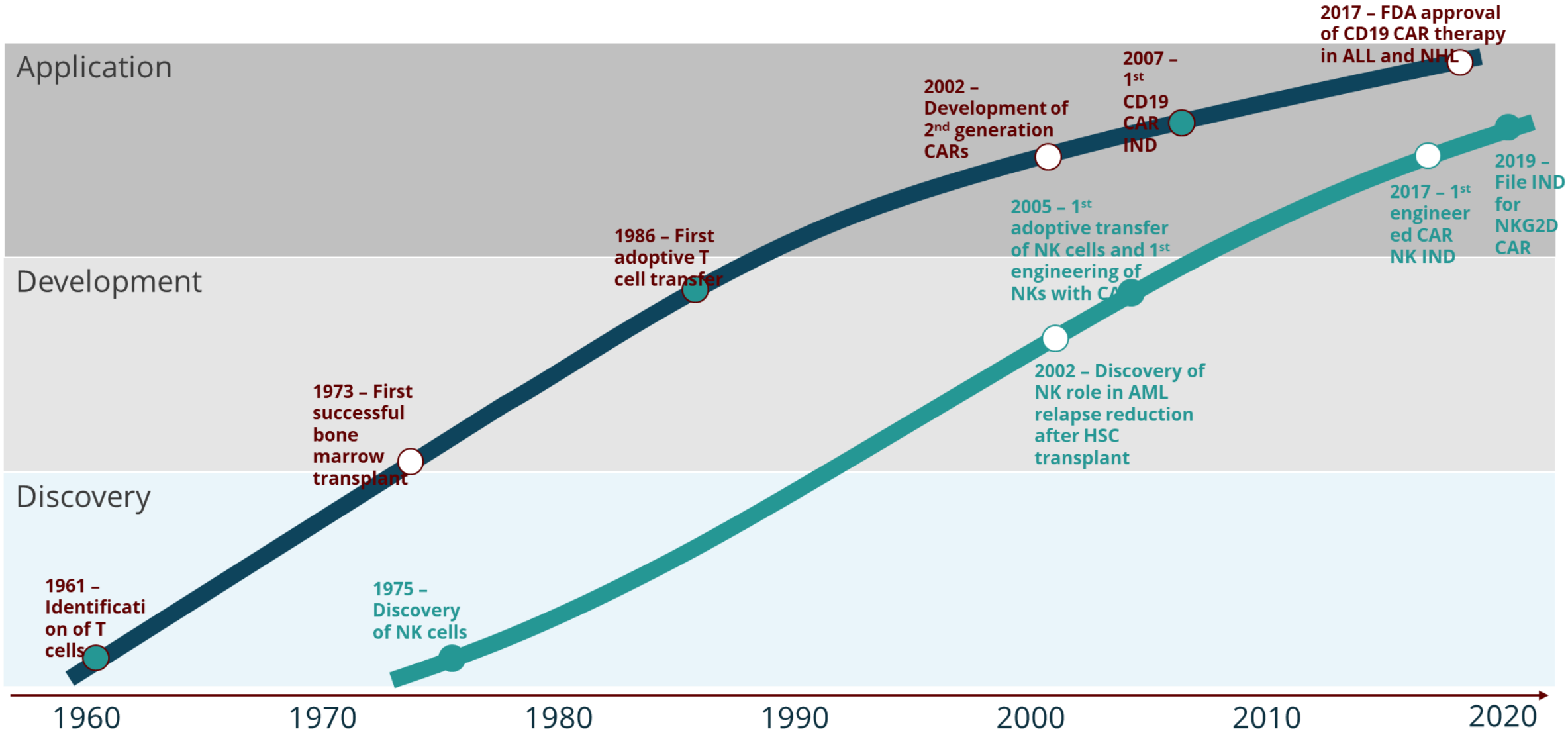
> Mismatching of donor-recipient inhibitory receptor subtypes provides off-the-shelf compatibility

Response rates in r/r AML with unmodified NKs

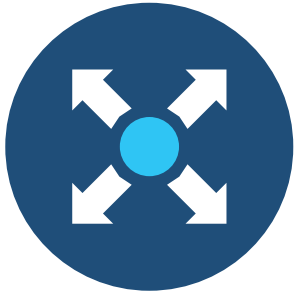
Study	Number of Subjects (N)	Response Rate, n (%)
Bachanova 2014, A+B cohort	42	9 (21.4)
Bachanova 2014, C cohort	15	8 (53.3)
Curti 2011	5	1 (20.0)
Kottaridis 2015	1	1 (100)
Miller 2005	19	5 (26.3)
Romee 2016	9	5 (56.6)
Rubnitz 2015	12	6 (50.0)
Average	*103*	*35 (34.0)*

Note: Data represented in the table above are aggregates at the trial level from the published literature reports. In trials that enrolled patients with both morphologic disease and complete remission at baseline, only results of former are included. AML responses include CR, CRi, sCR and MLFS as reported by individual trials.

Natural killer cell therapy: Following in the footsteps of T cells



Nkarta technologies for maximizing NK cell potential



Expansion

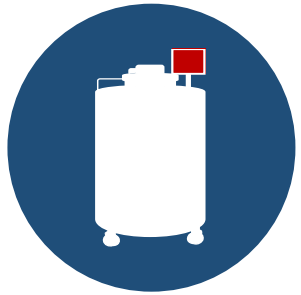
Co-culture with stimulatory cell line to achieve high cell doses

Persistence

Expression of membrane bound IL-15 to enhance time in circulation

Targeting

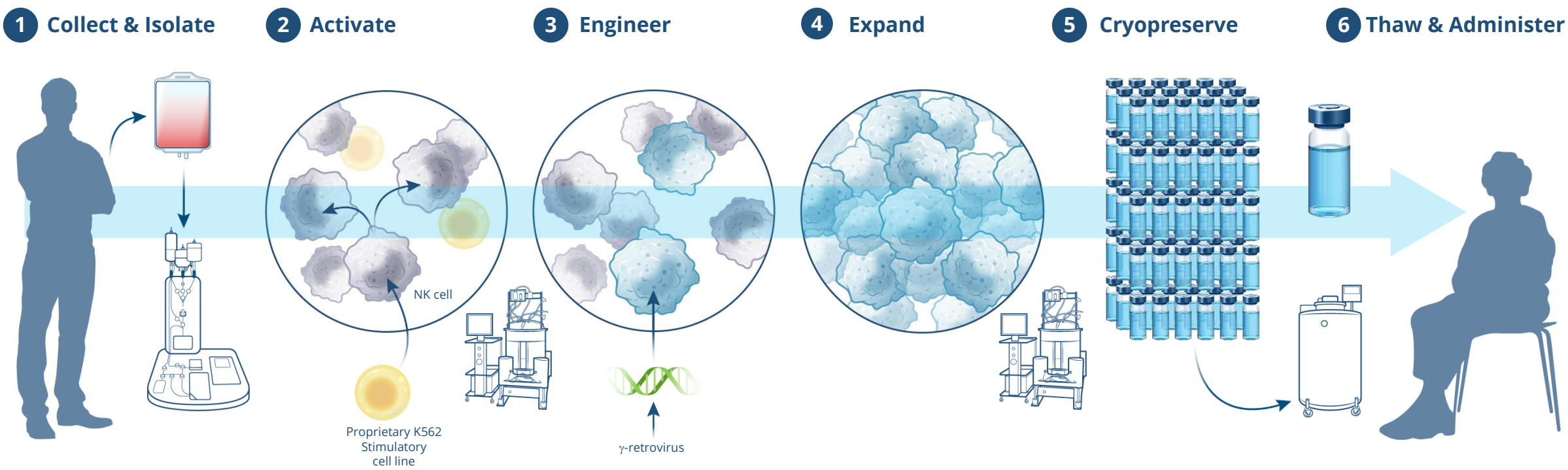
Engineered for expression of optimized CARs



Cryopreservation

Maintains NK viability and potency

Allogeneic, commercially-enabling manufacturing



NK cells collected from healthy donors by leukapheresis.

NK cell expansion using proprietary stimulatory cells.

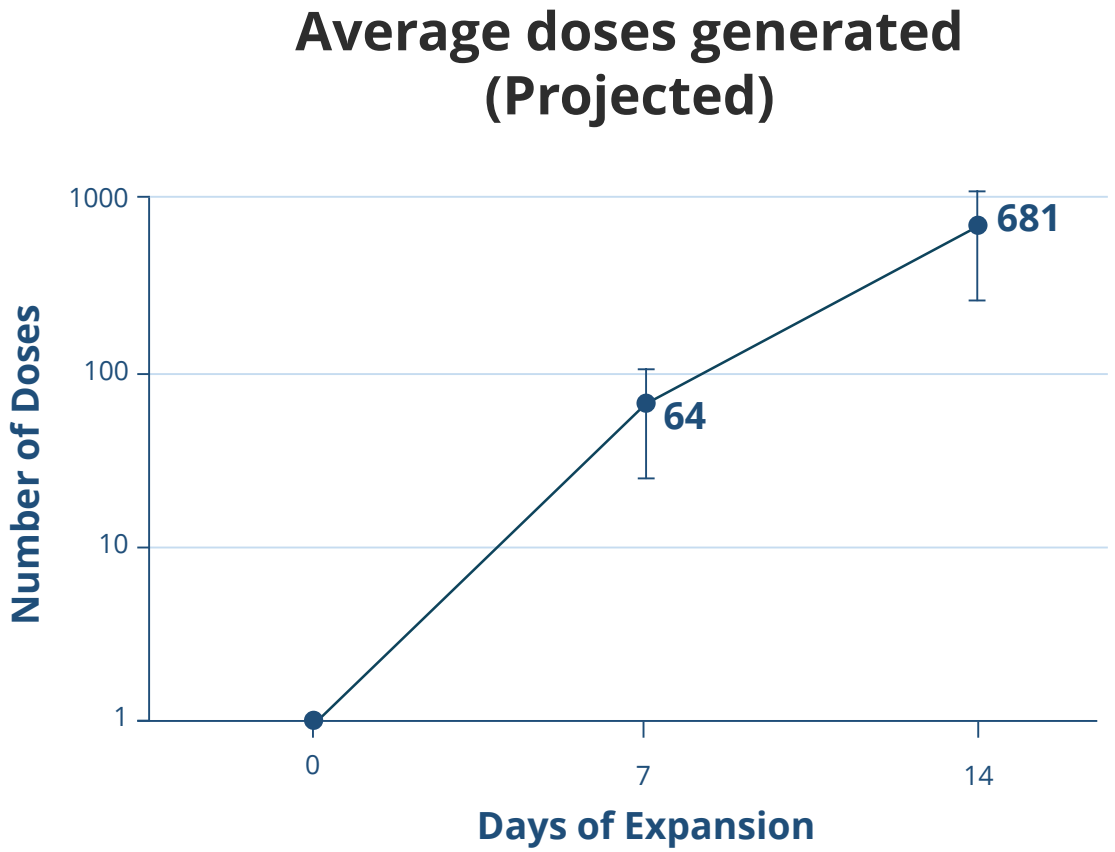
Expanded NK cells are transduced to express mbIL-15 and CAR.

Continued expansion driven by mbIL-15.

Harvesting and cryopreservation of final cell product.

NK product candidate is thawed for off-the-shelf administration to patients.

Expansion on stimulatory cells enables large scale manufacturing

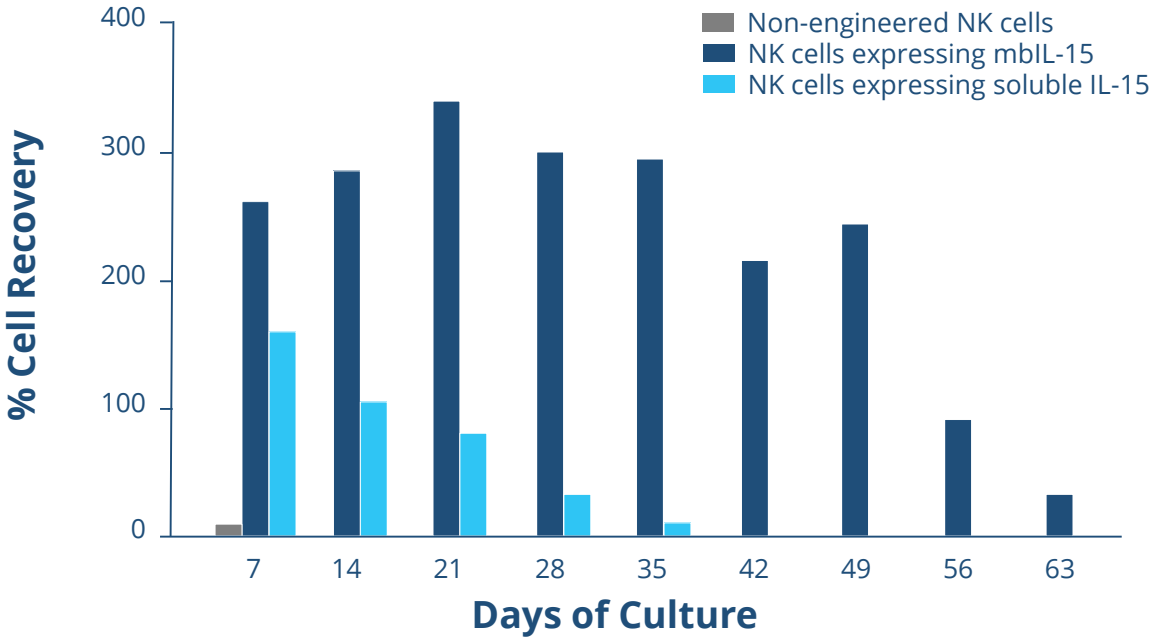


Data above are an average of 62 expansions from 18 different donors. Assumed dose is 10^9 CAR-NK cells, the highest contemplated in the NKX101 heme Phase 1 trial.

- Expansion technology used in 6 clinical trials (non-engineered NKs)
- Extensive optimization enables truly off-the-shelf products
- Currently constructing in-house GMP manufacturing suite

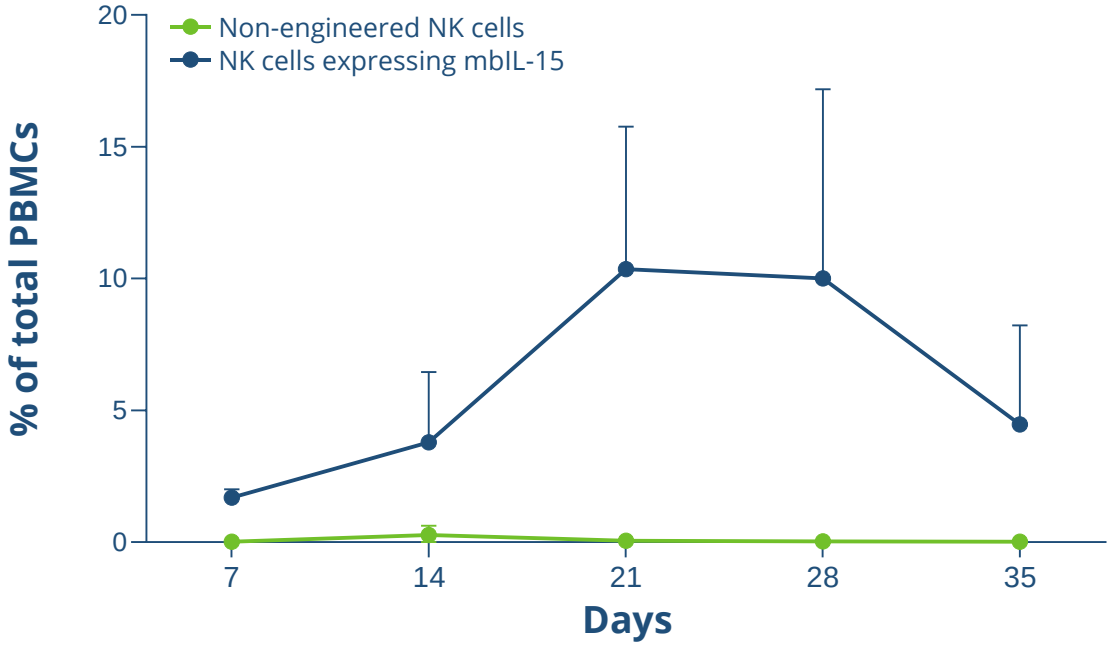
Superior persistence from membrane bound IL-15

In vitro persistence



Source: Imamura, Blood 2014

In vivo persistence and expansion in NSG mice



Source: Nkarta. N = 5 per arm.

NK cells engineered to express membrane-bound IL-15 (mbIL-15) demonstrate superior persistence as compared to unmodified NK cells

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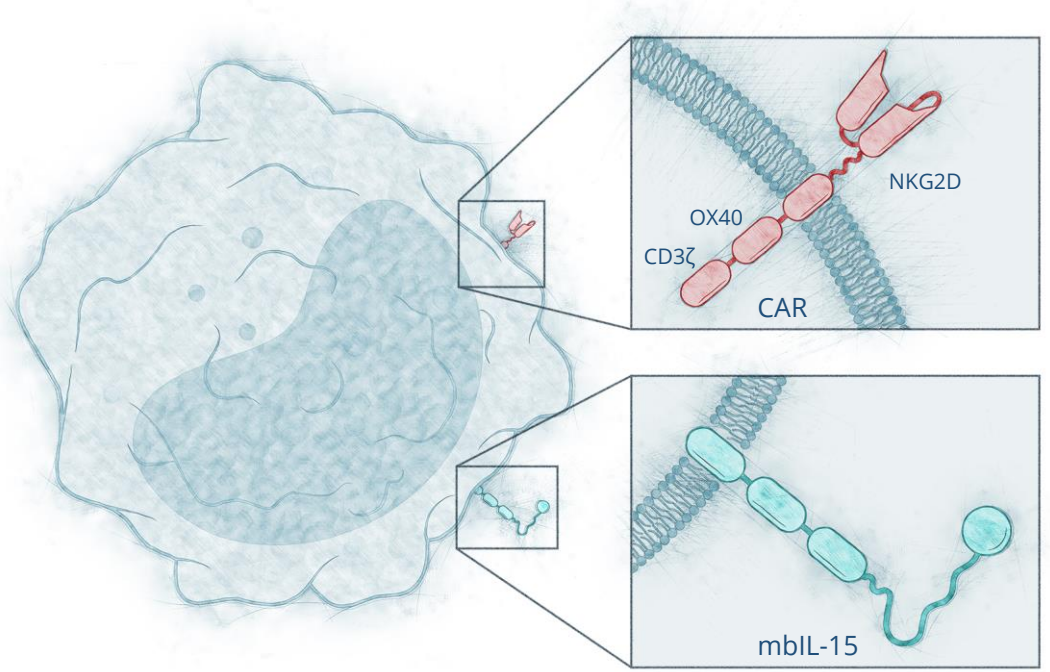
NKX101

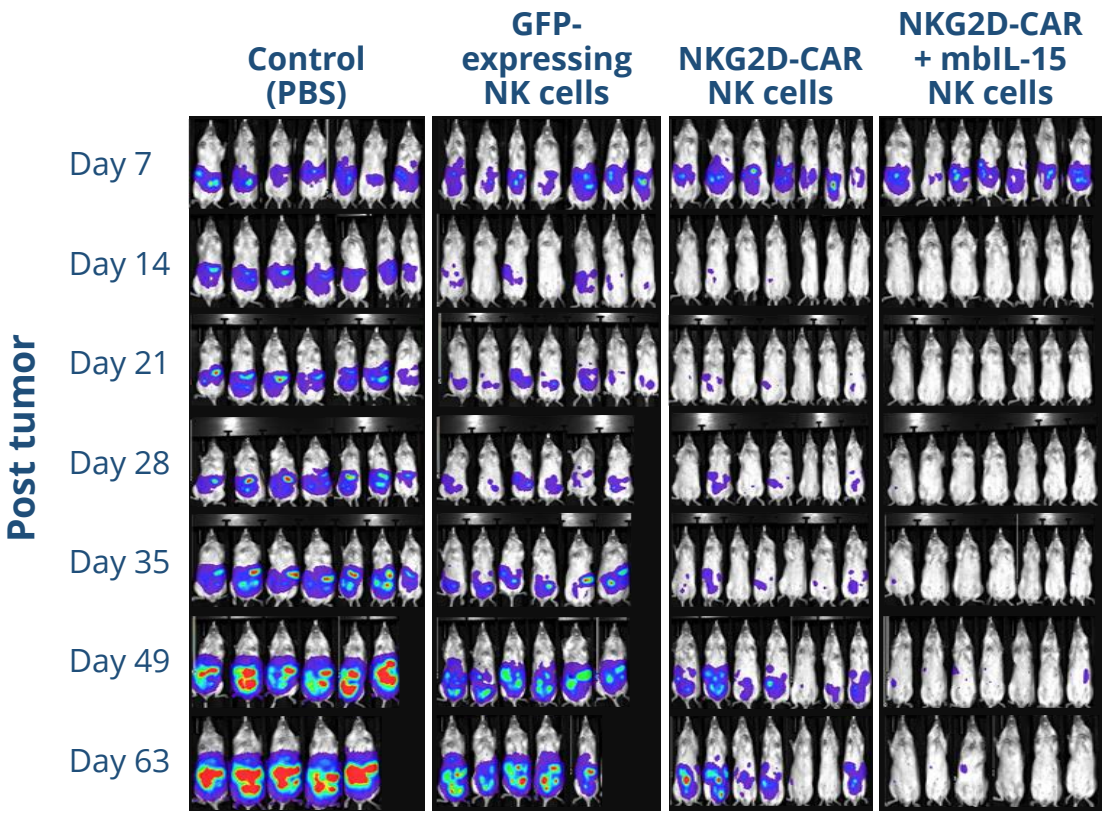
NKX101: next generation CAR-NK targeting NKG2D ligands

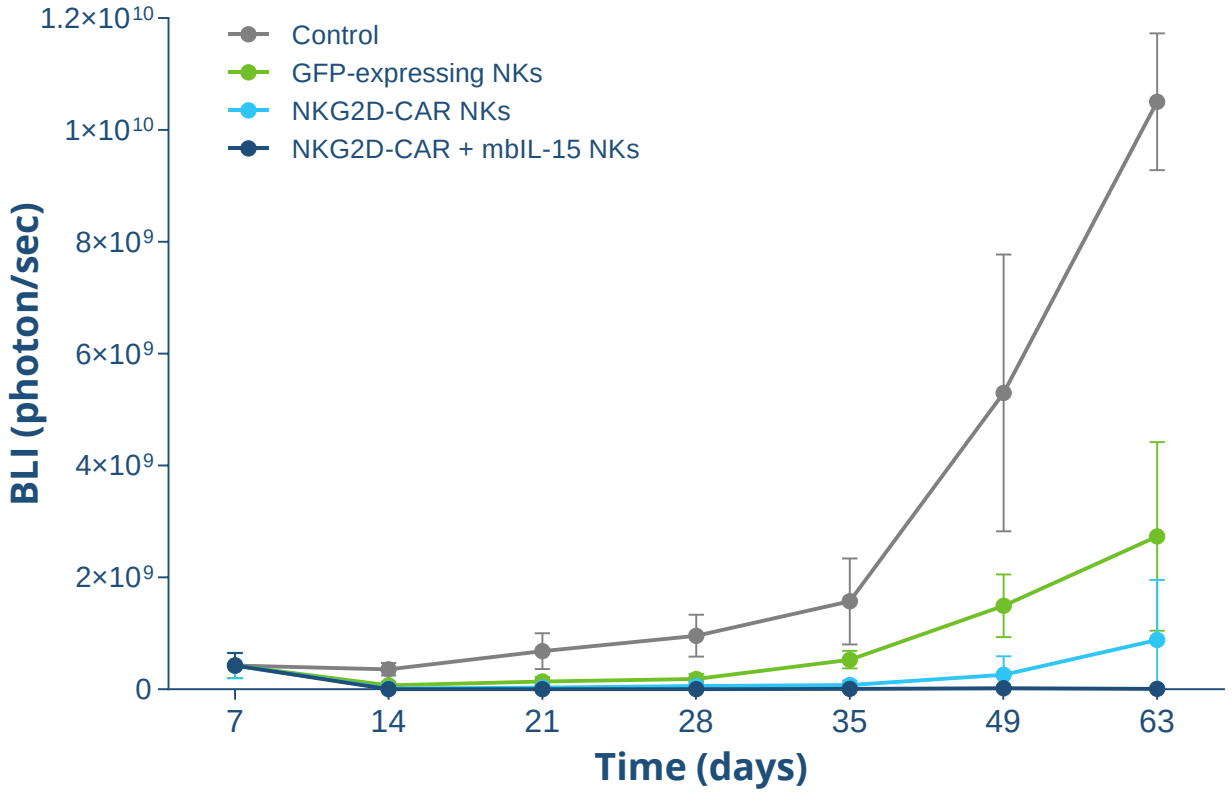
- NK activation and tumor killing largely driven by NKG2D receptor
- Targets of NKG2D are selectively over-expressed in cancer cells
- >10x increase in NKG2D expression vs. non-engineered NK cells
- OX40 costimulatory domain



NKX101: NKG2D activating receptor, OX40 costimulatory domain, CD3ζ signaling moiety, membrane bound IL-15

Co-expression of an NKG2D CAR and mbIL-15 maximizes anti-tumor activity

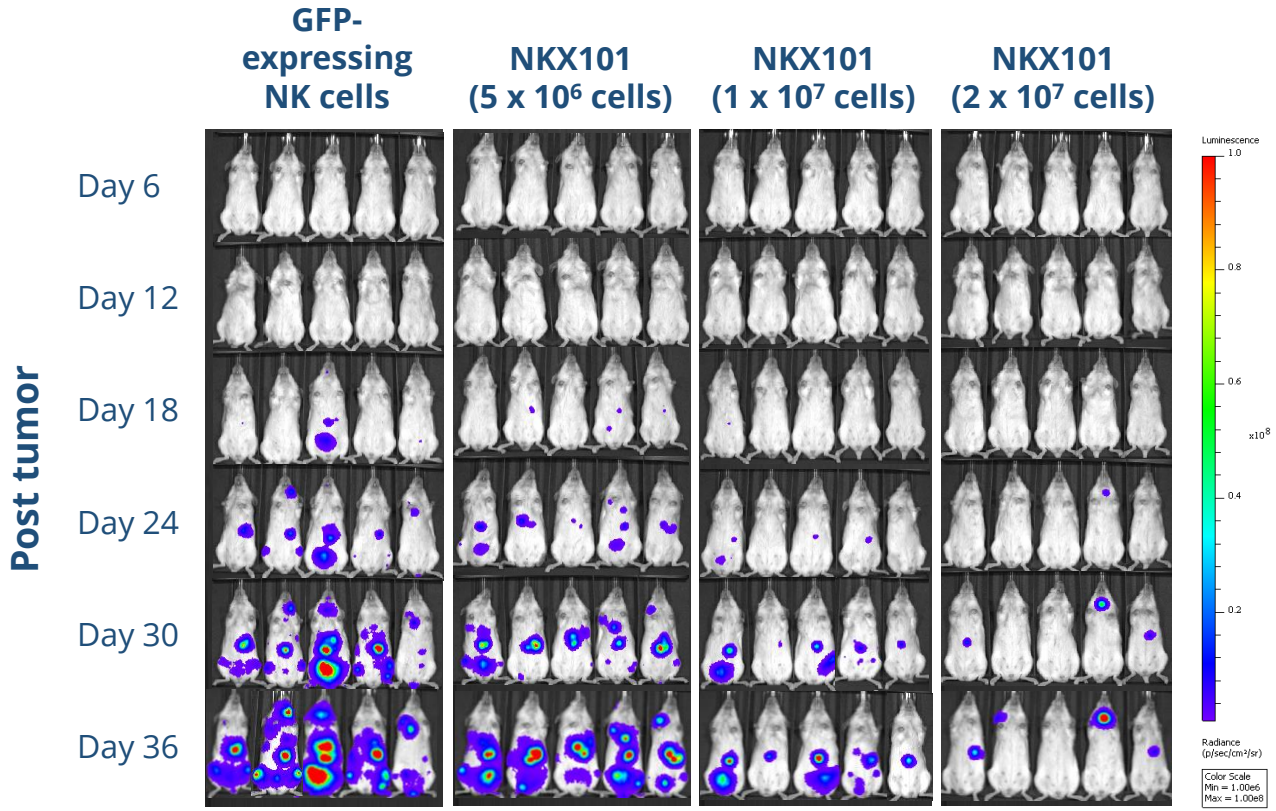




U2OS osteosarcoma model; 3 x 10^6 NK cells administered on D7. Graphical data at right are average BLI of mice above.

NKX101: Acute myeloid leukemia (AML)

- AML US incidence: ~21K / yr
  - 5-year survival rate ~28%
- NKG2D targets are over-expressed in AML blasts
- Clinical activity with non-engineered NKs



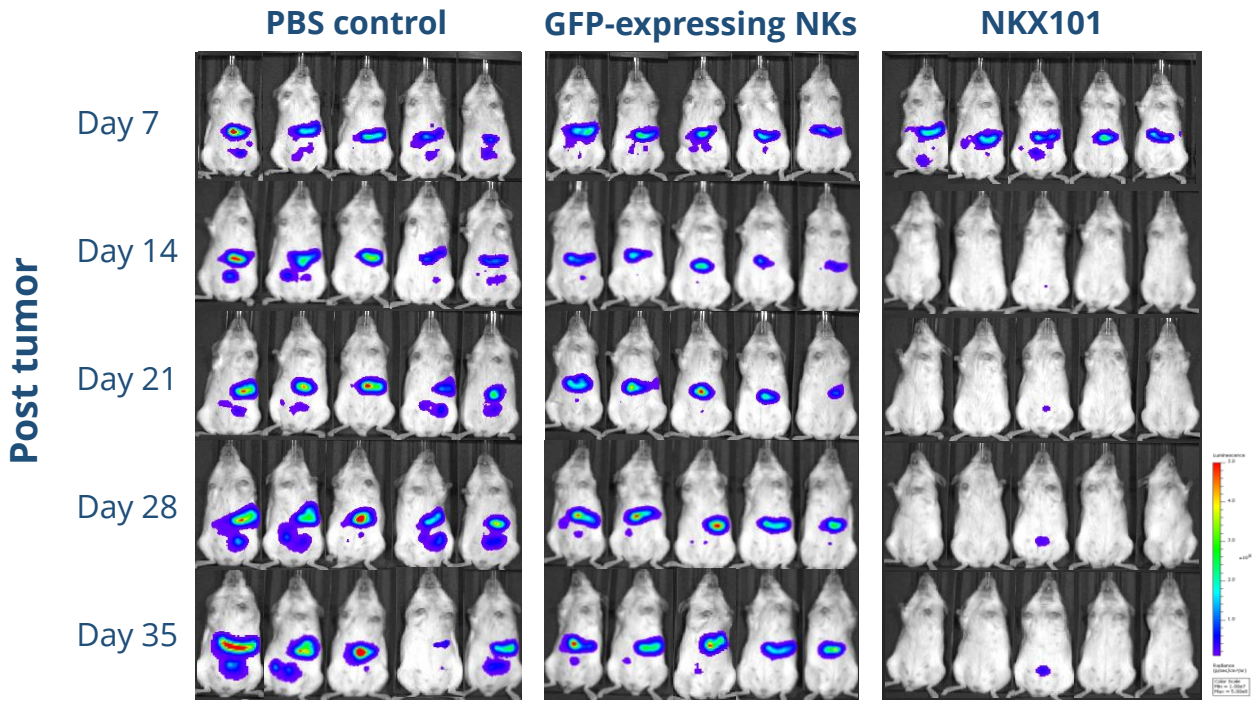
THP-1 xenograft model treated with a single dose of NK cells (i.v.) 2 days after tumor injection

Sources: SEER database; Veluchamy, Front Immunol 2017; Brayer ASH 2018; Hilpert, J Immunol, 2012

NKX101: Solid tumors

- Liver & bile cancer US incidence: ~42K / yr
  - 5-year survival rate ~18%
- NKG2D targets over-expressed on HCC and CRC cells
- NK cells are important in liver immunity and tumor surveillance
- Phase 1: Locoregional delivery using SOC technique in 1° liver cancer or liver metastases

NKX101 activity in NSG mice



SNU449 HCC xenograft model
3 x 10^6 NK cells injected at day 7 post-tumor

HCC: Hepatocellular carcinoma. CRC: Colorectal cancer. Sources: SEER database; Sun Act Pharm Sin 2015; Kamimura, J Hepatology, 2012; Kamiya et. al, Cancer Immunol Res 2016; Qin 2017

Overall summary

- Engineered NK cells can be produced at large scale, consistent with off-the-shelf applications
- Nkarta's lead product NKX101 demonstrate robust activity in both *in vitro* and *in vivo* models
- Further refinements of the platform are possible via gene editing approaches