Natural Killer cells and Hematopoietic Stem Cell Transplantation

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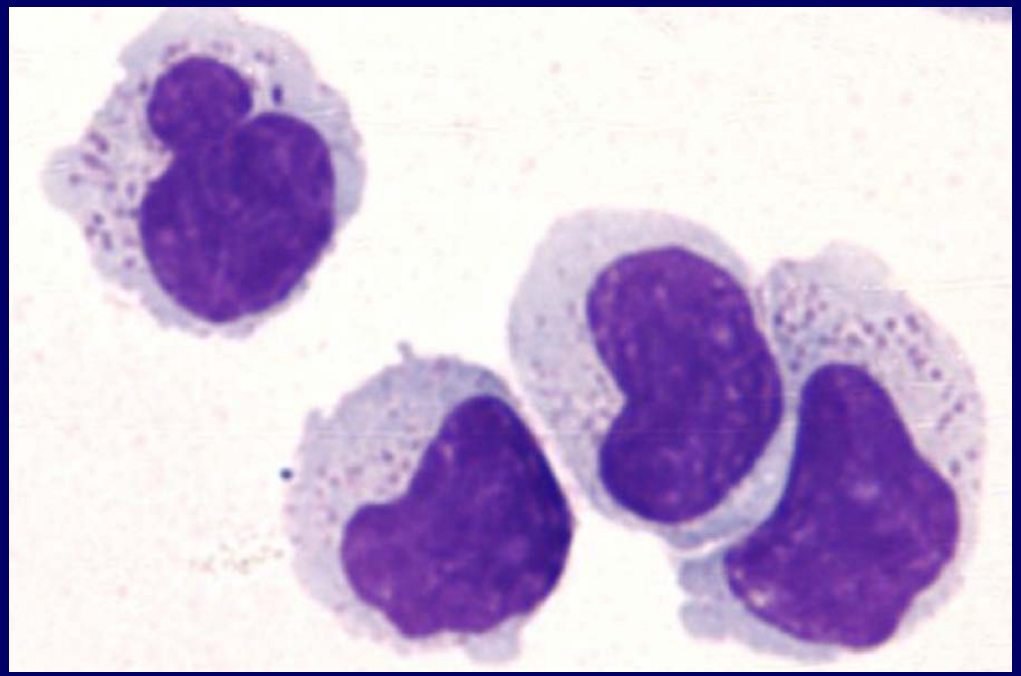
NK cells are important

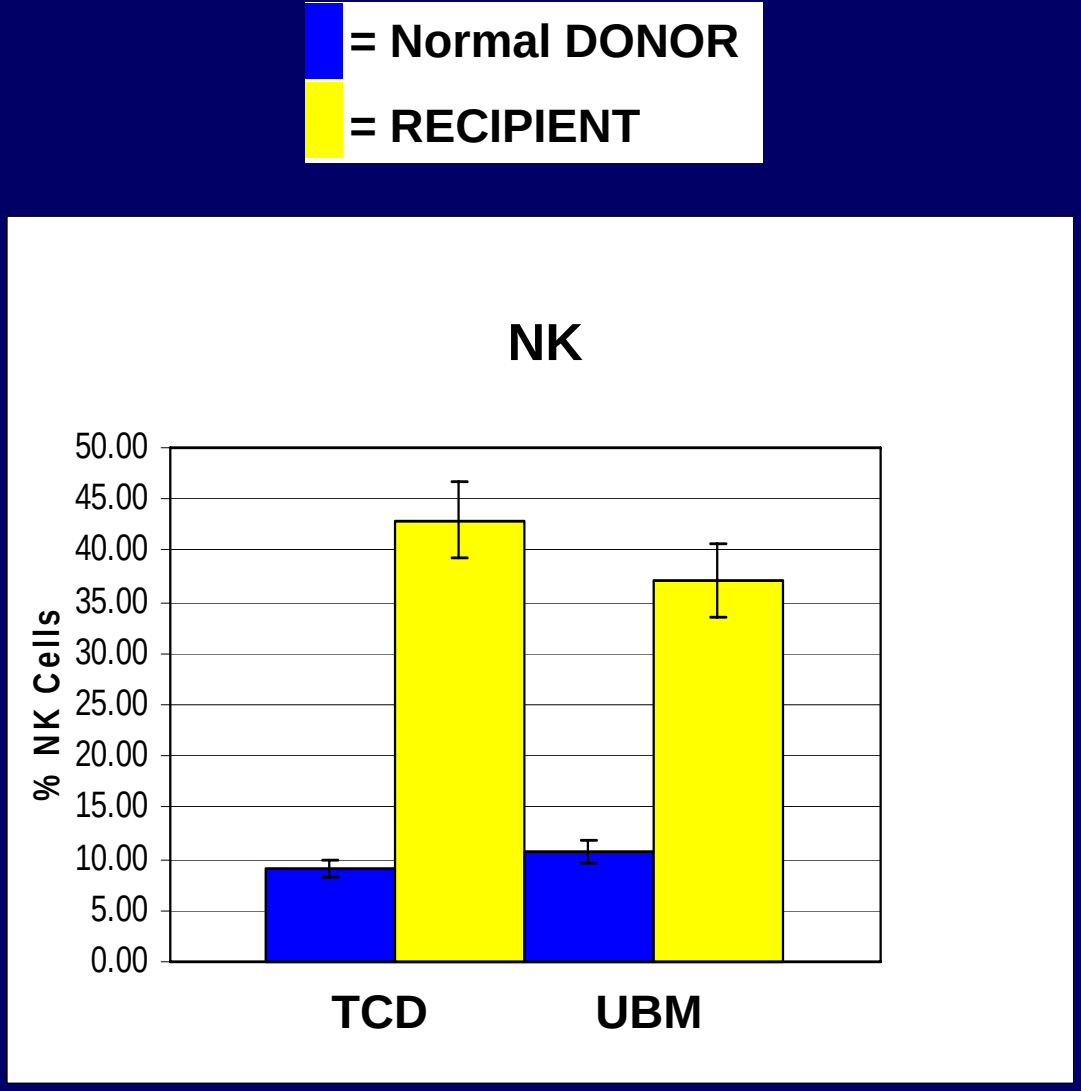


- Cancer treatment and tumor surveillance
- Infection disease control
- Autoimmunity
- Pregnancy (placental angiogenesis)

NK cell functions

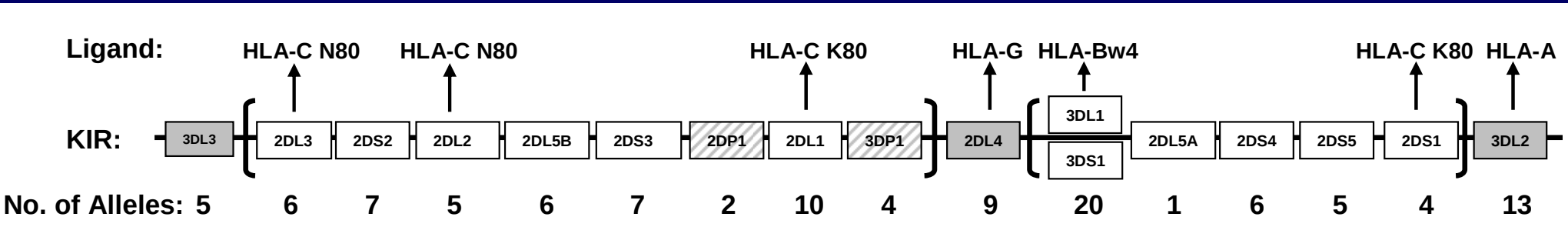
- Killing targets
- Produce cytokines
  - Interferon-γ
  - Tumor necrosis factor
  - Many others

NK cells after transplant are increased



Cooley et al
Blood 106:4370, 2005

Chr. 19 determines the personality of NK cells: Killer-immunoglobulin receptor (KIR) gene locus



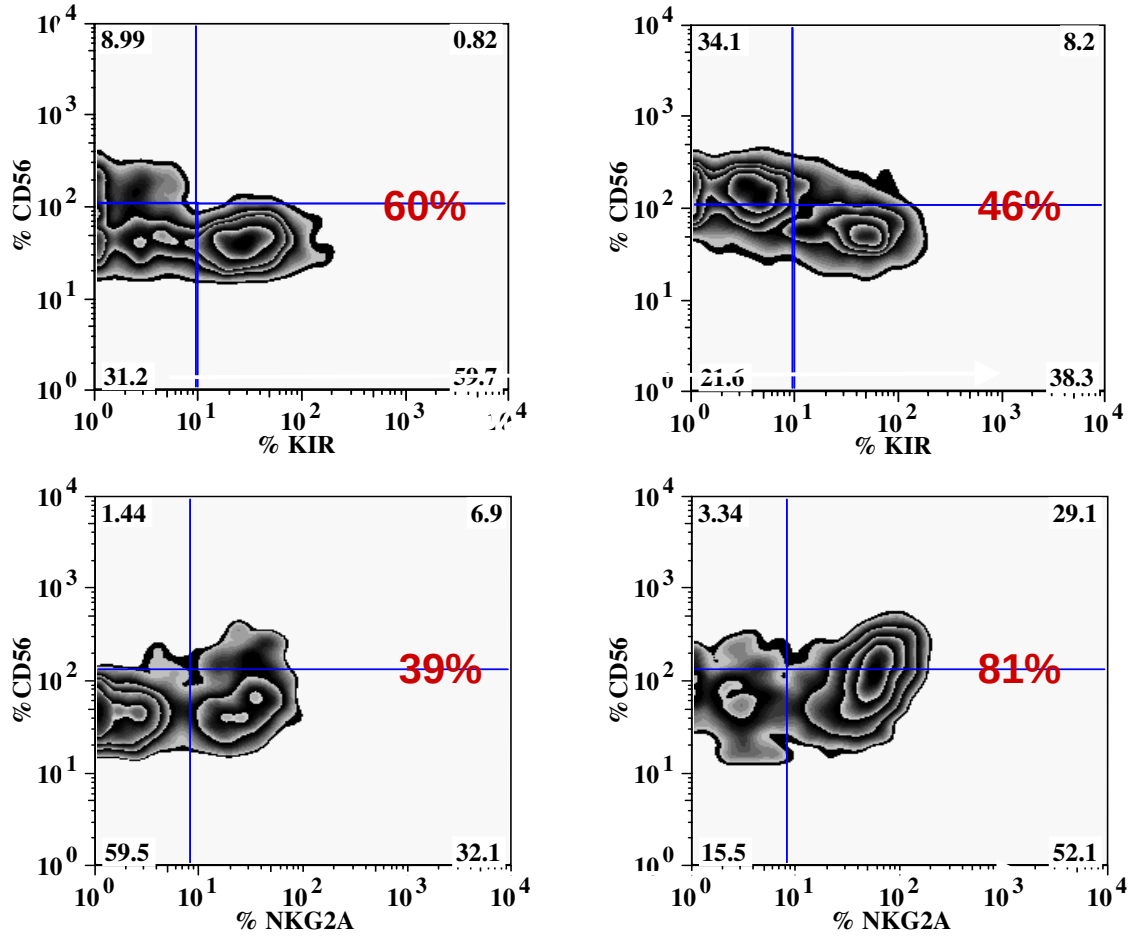
NKG2 family recognizes HLA-E

From Peter Parham

NK cells are very different after URD HCT

Donor

Recipient

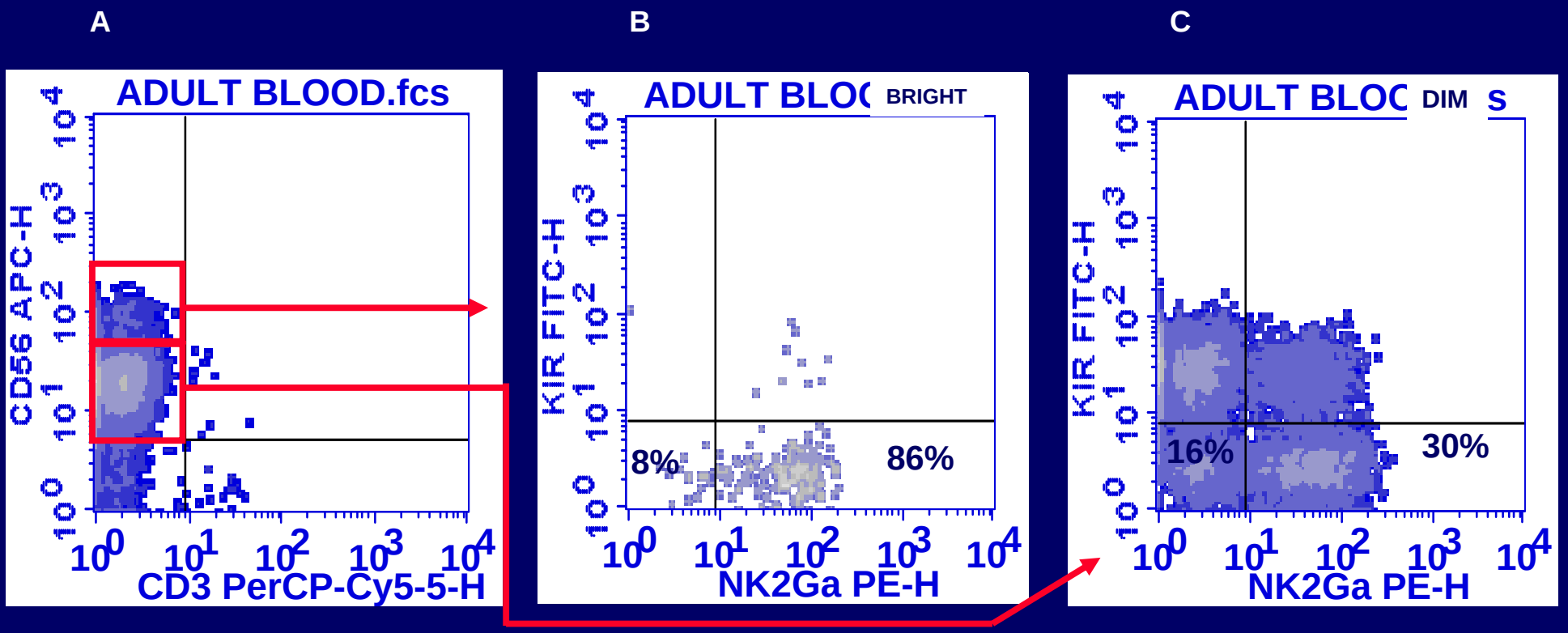


Recipients have

- < KIR
- > CD56$^{+bright}$
- > NKG2A
- < Function

Cooley et al
Blood 110:578, 2007.

NKG2A/KIR expression distinguishes populations of CD56^{+dim} NK cells

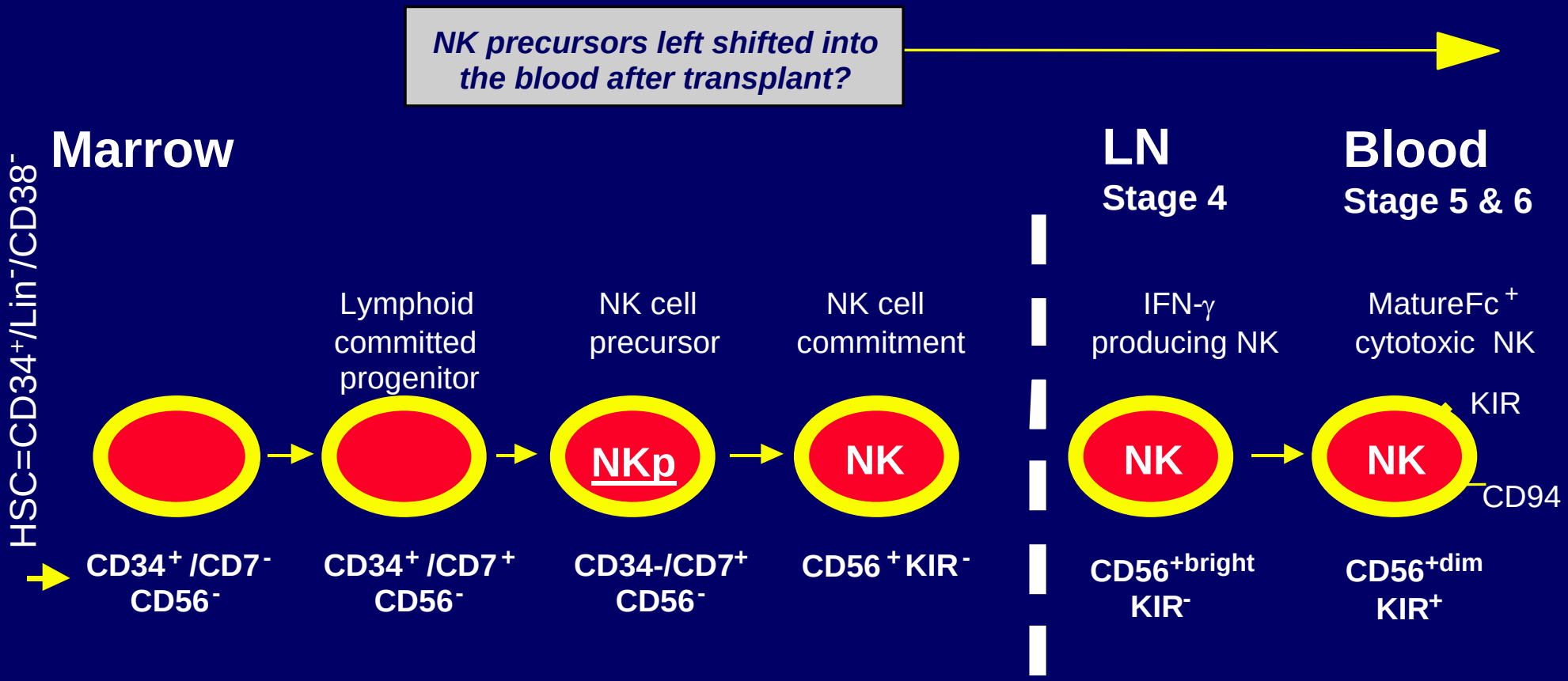


KIR^{-}/NKG2A^{-} subset: 19.4 ± 2.8% of CD56^{+dim} NK cells healthy donors (n=26)

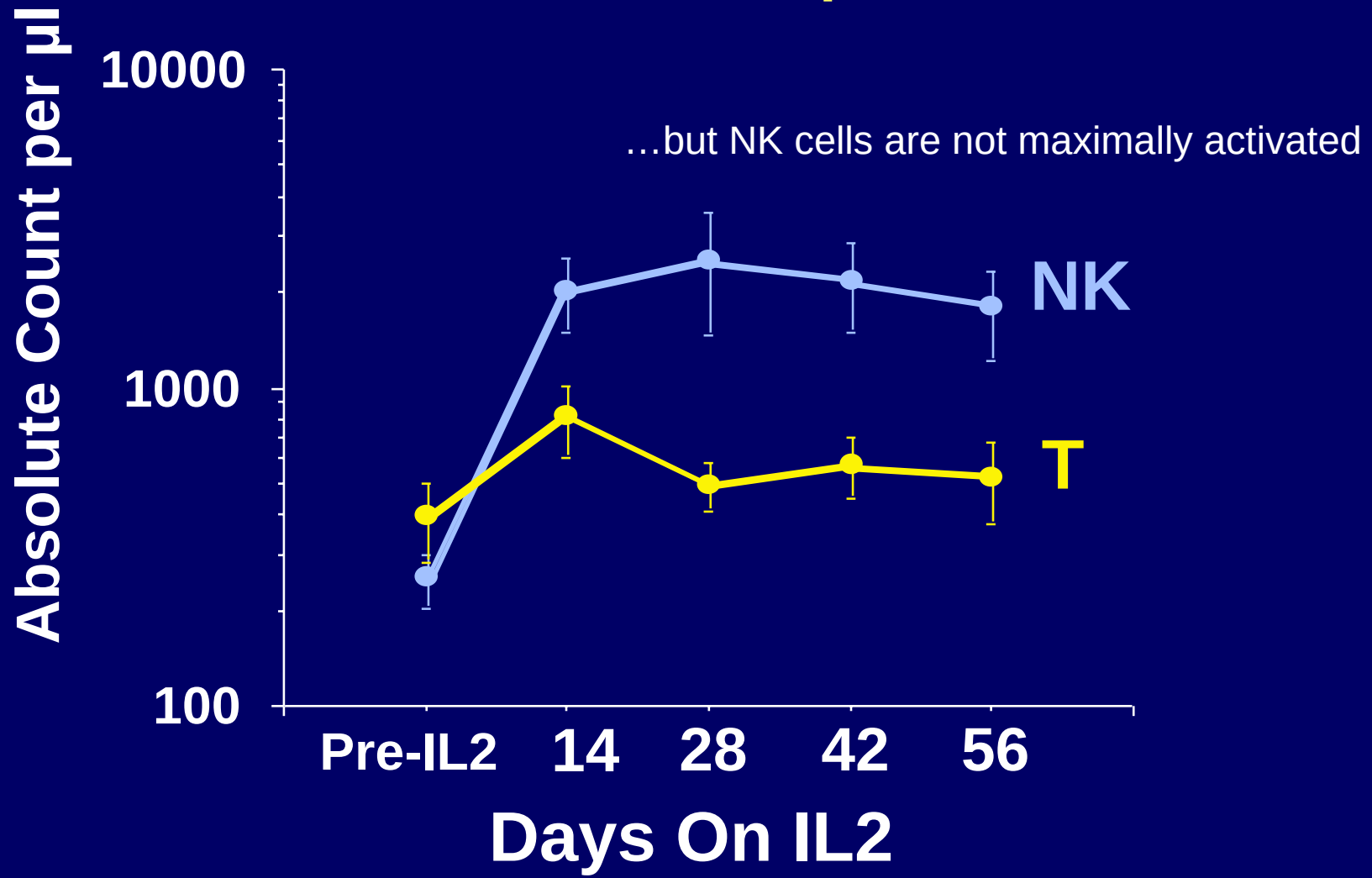
These cells do not kill targets or make IFN, thus are hyporesponsive (immature)

Cooley et al Blood 110:578, 2007.

Hypothesized NK cell development schema

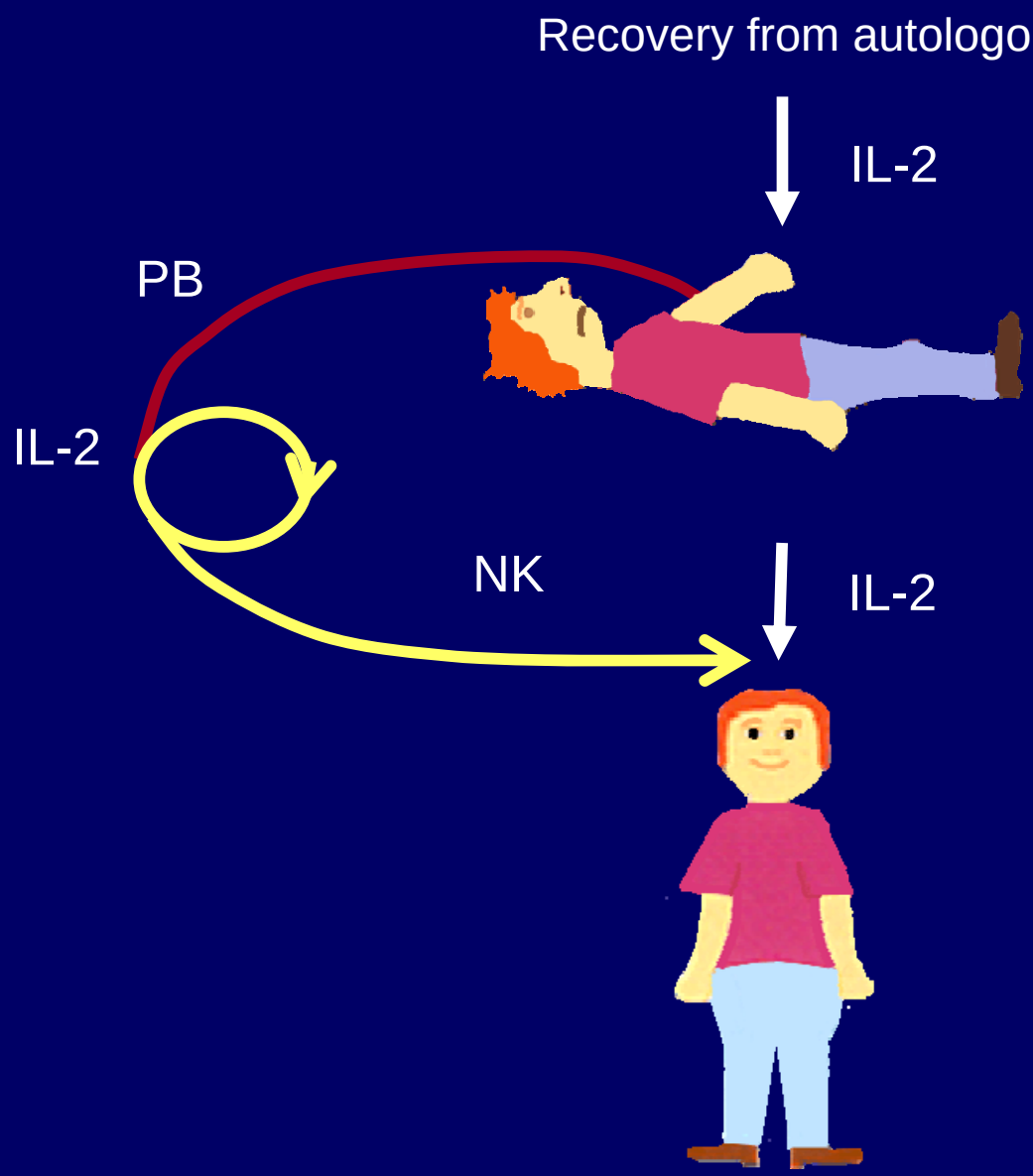


Outpatient subcutaneous IL-2 promotes in vivo NK cell expansion



Miller et al, Biol Blood Marrow Transplant 3:34, 1997

Autologous NK Administration in Cancer Patients



NK cells more activated using this approach

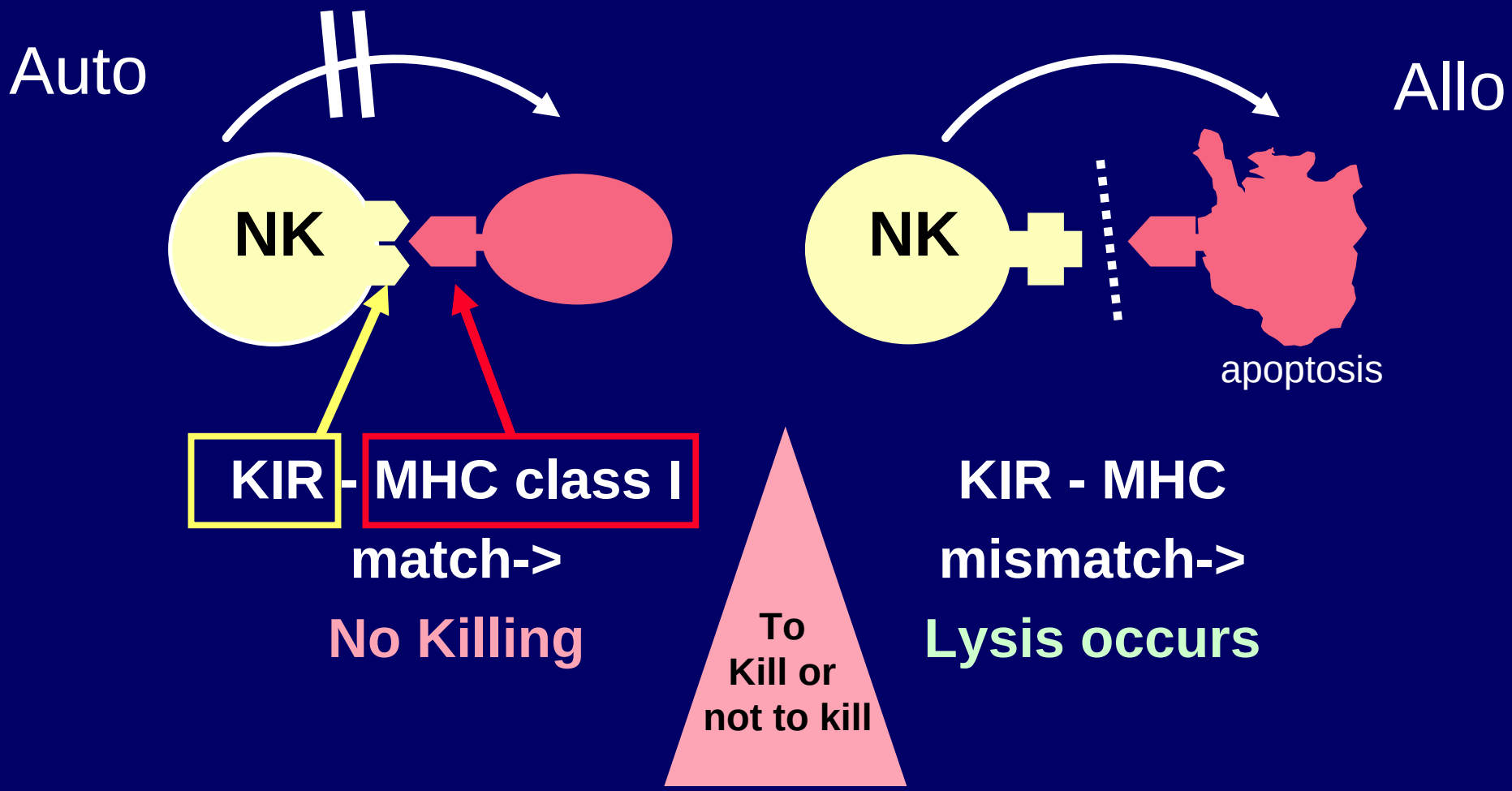
NK cell-based autologous Immunotherapy to prevent relapse (HD, NHL, BC)

Burns et al, **Bone Marrow Transplant, 32:177-186, 2003**

Conclusions

- **Enhanced activation of NK cells.**
- **A matched paired analysis with our data and data from the IBMTR showed no apparent efficacy (survival or time to disease progression).**

Hypothesis: Autologous NK cell therapy failed due to inhibitory receptors that recognize MHC

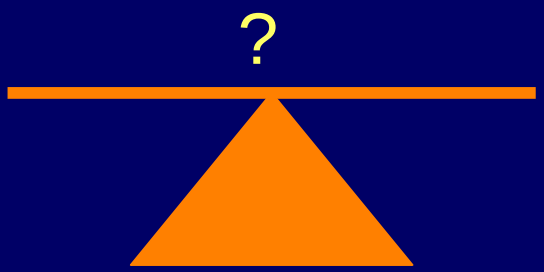


AML Transplant trials based on promoting NK cell alloreactivity

	Transplant	Graft	Outcome
Ruggeri *et al* Science 3/2002	Haploidentical KIR-L Mismatch	TCD	Benefit in AML
Davies *et al* Blood 11/2002	URD KIR-L Mismatch	UBM	No Benefit
Giebel *et al* Blood 8/2003	URD KIR-L Mismatch	*In Vivo* TCD	Benefit

How can we best exploit NK cells?

Adoptive Transfer



Transplant

Pros and cons

Safer

Transient

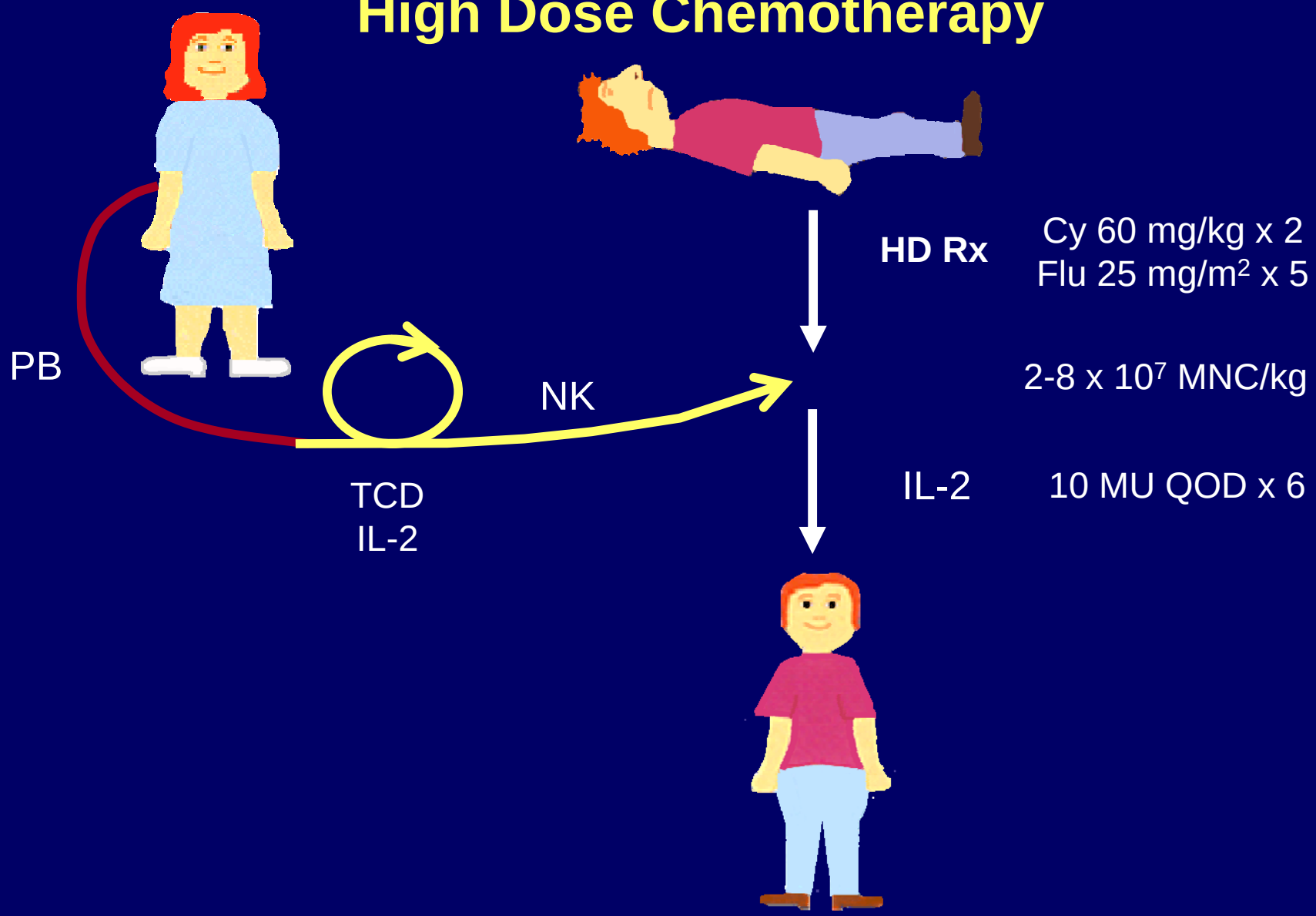
Can expand in vivo (IL-2)

More TRM

Permanent

Too risky 2^{o} GVHD risk

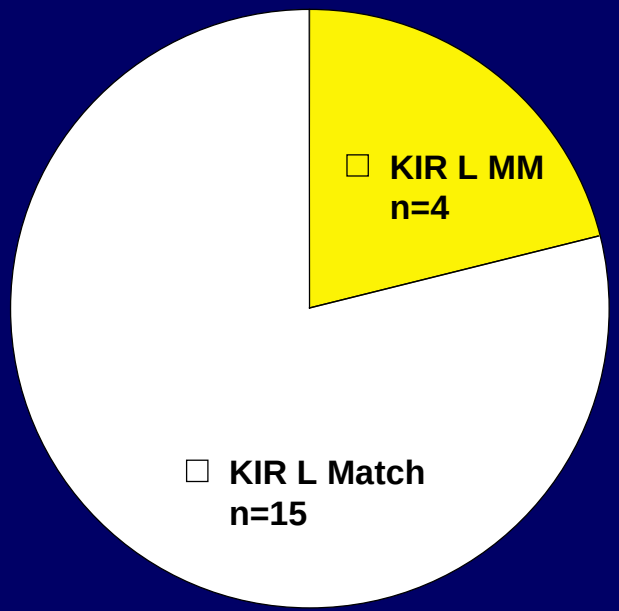
Related Donor Haploidentical NK Infusions After High Dose Chemotherapy

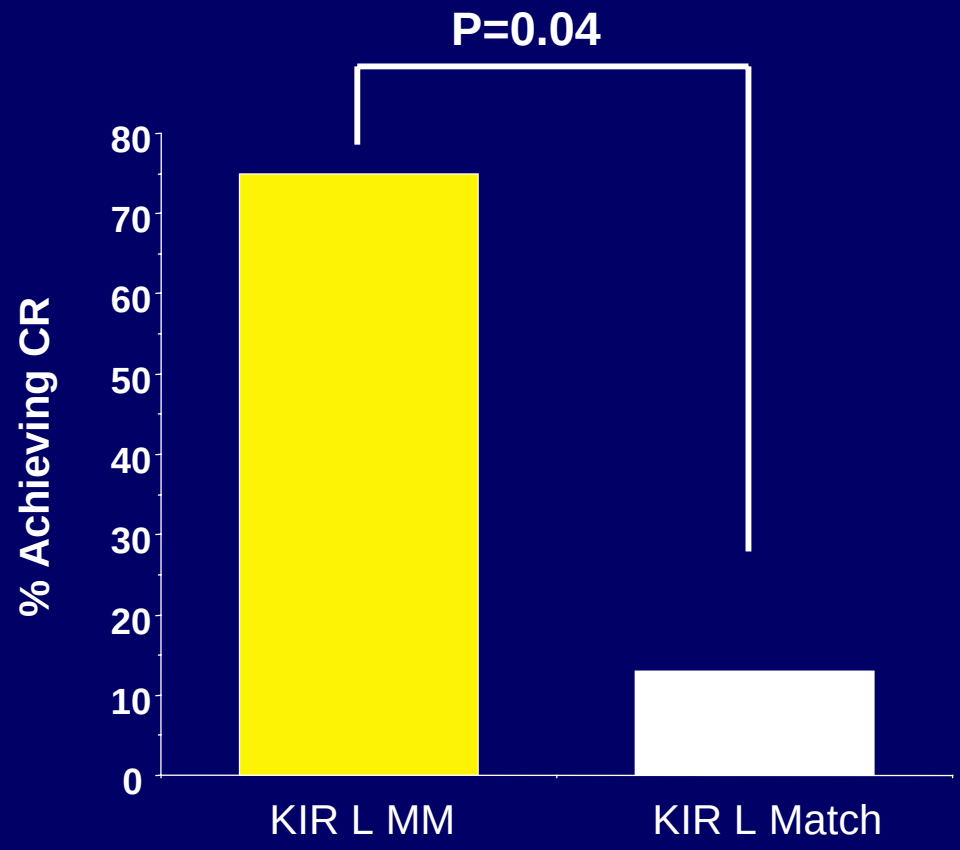


Patients and eligibility

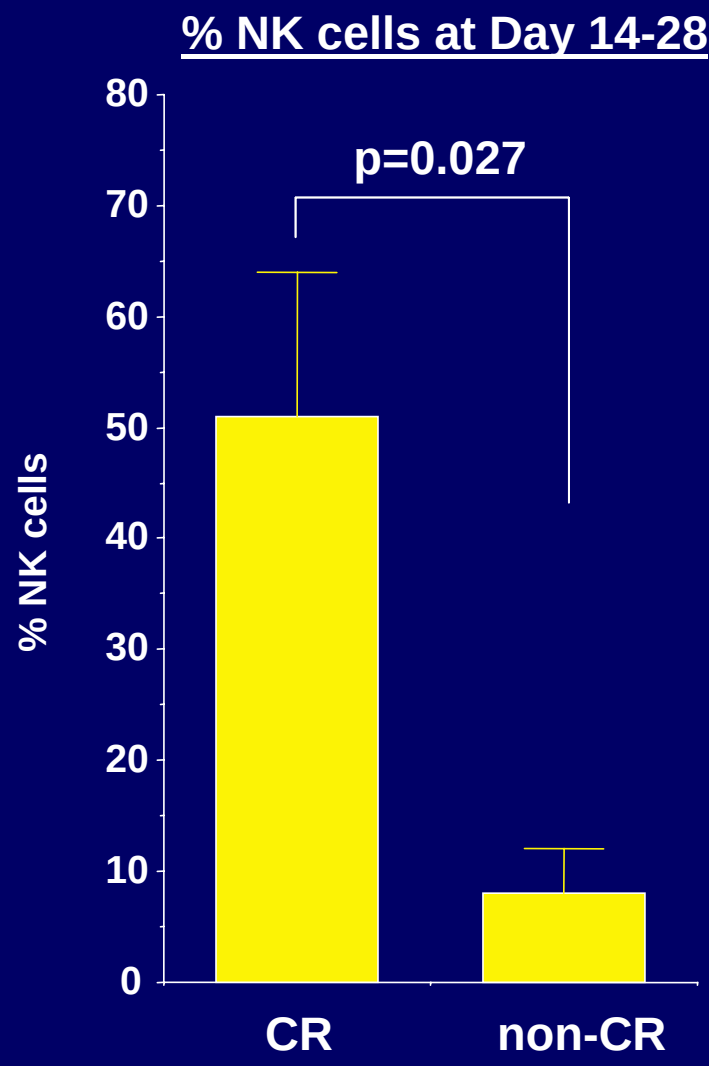
- Poor prognosis AML (n=19)
  - Primary refractory disease
  - Relapsed disease not in CR after 1 or more cycles of standard re-induction therapy
  - Secondary AML from MDS
  - Relapsed AML $\geq$ 3 months after HCT.
- No active infections

KIR Ligand mismatched donor correlates with achieving AML CR (5 of 19=26%)





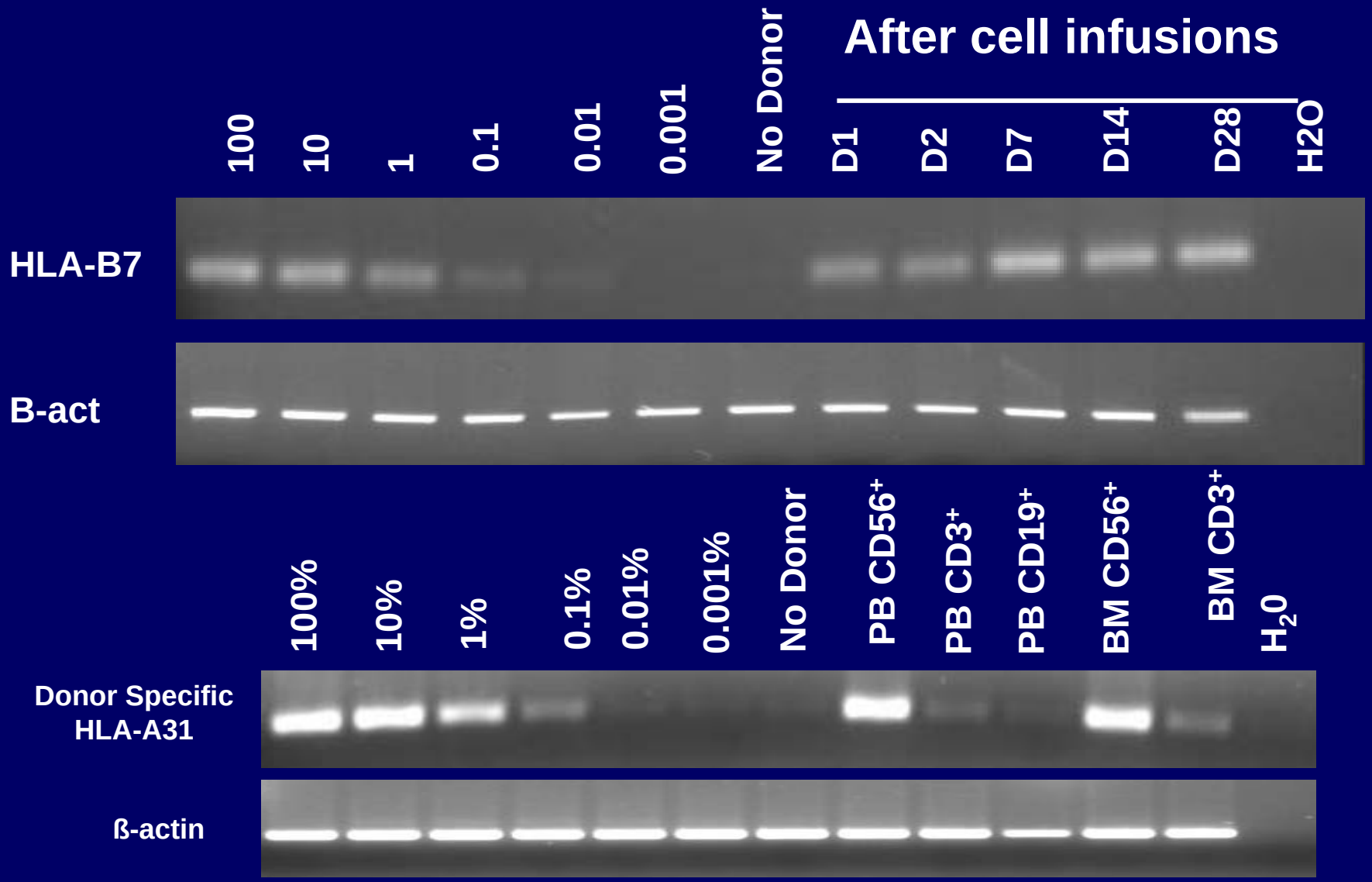
CR patients had higher numbers of functional NK cells after haplo NK cells



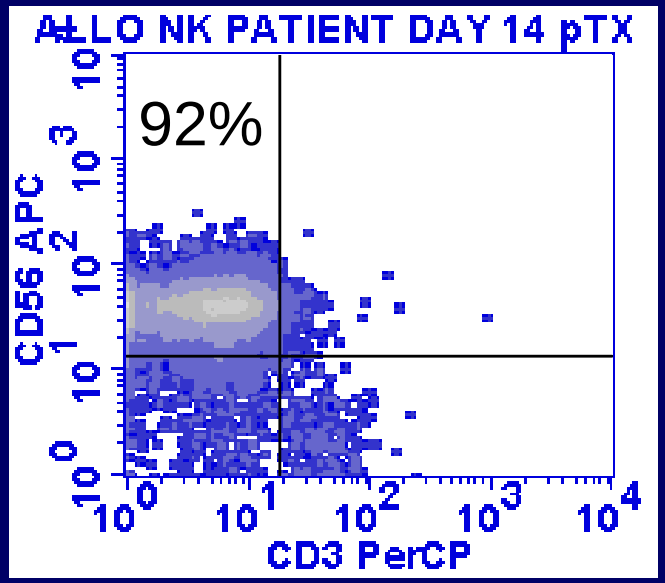
NK cells did not expand with lower dose preparative regimens

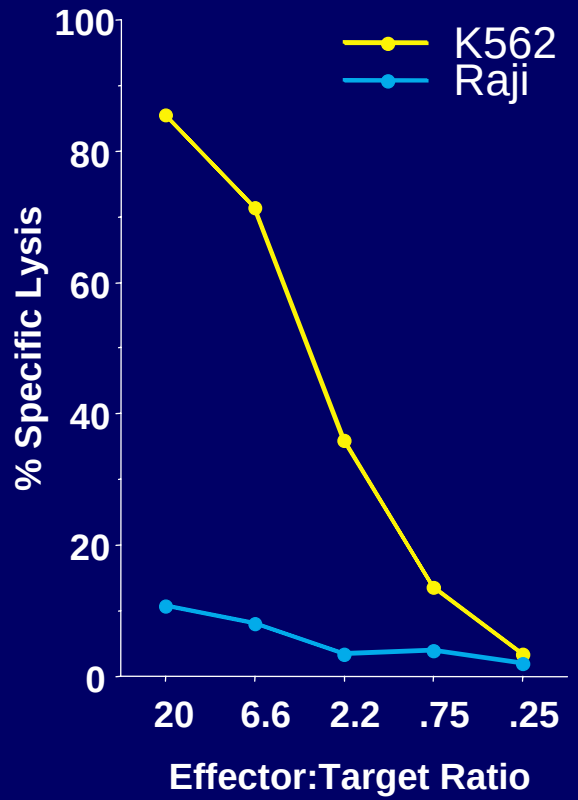
Miller et al, Blood 105:3051, 2005

In vivo expansion of haploidentical NK cells in AML



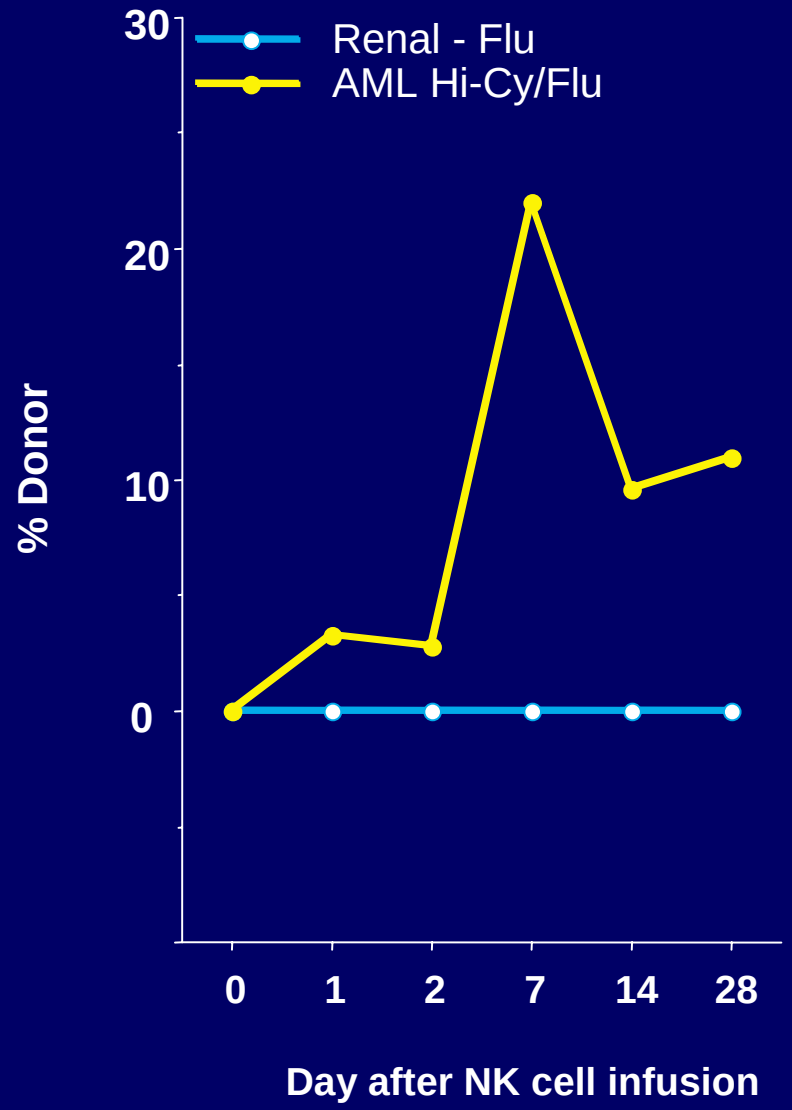
Circulating donor cells were functional NK cells 14 days after Haplo NK cell infusions



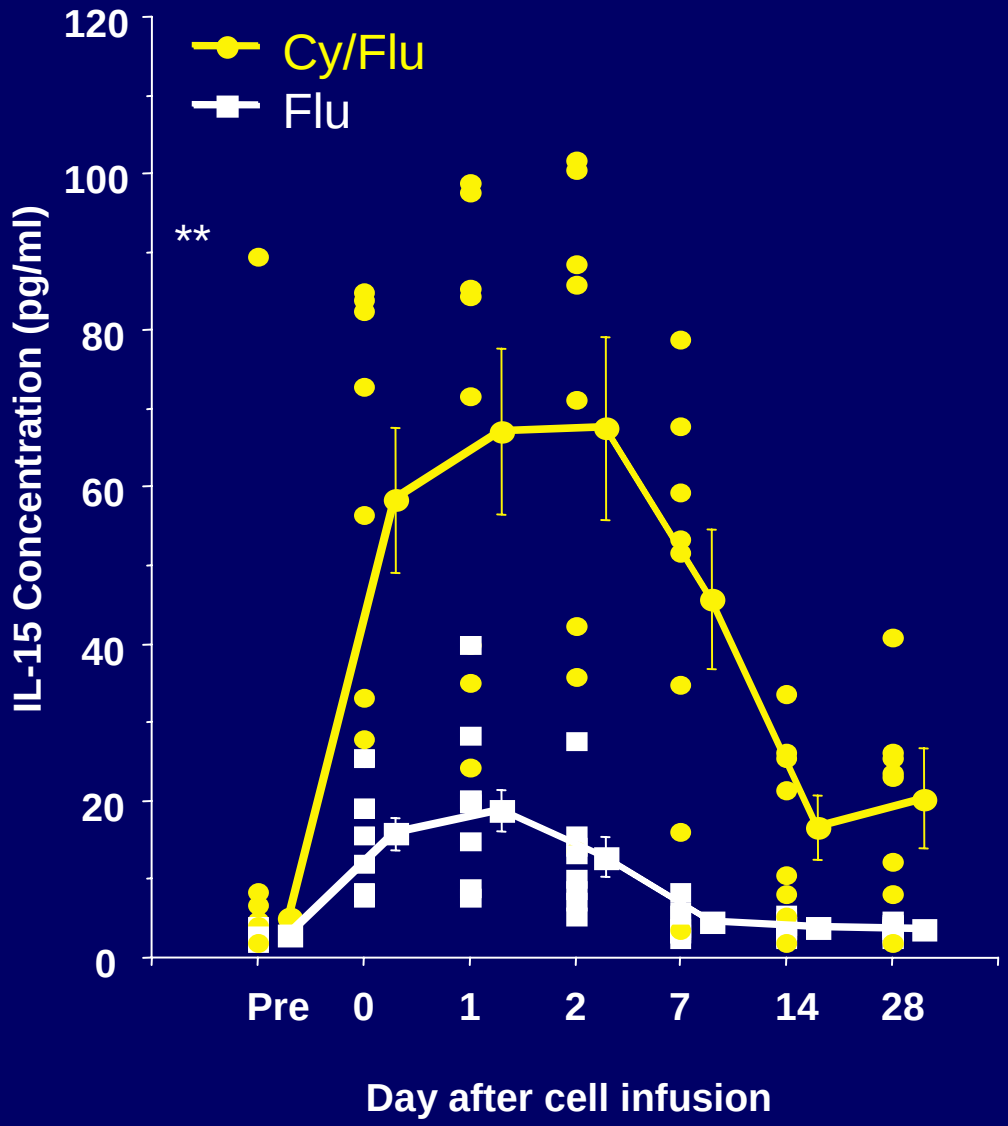


Verified by VNTR and G-banding

Hi-Cy/Flu induces in vivo expansion of donor cells (all patients by prep)



Hi-Cy/Flu induces endogenous IL-15 which correlates with *in vivo* NK cell expansion



Interpretation of cytokine data

- Every time we give lymphodepleting chemotherapy (±TBI), we see a sustained surge in endogenous IL-7 and IL-15
- May explain high fevers when adding exogenous IL-2 in this setting.

Questions

- Why NK cells don’t expand in everyone?
- Would other cell sources be superior to adult blood NK cells?

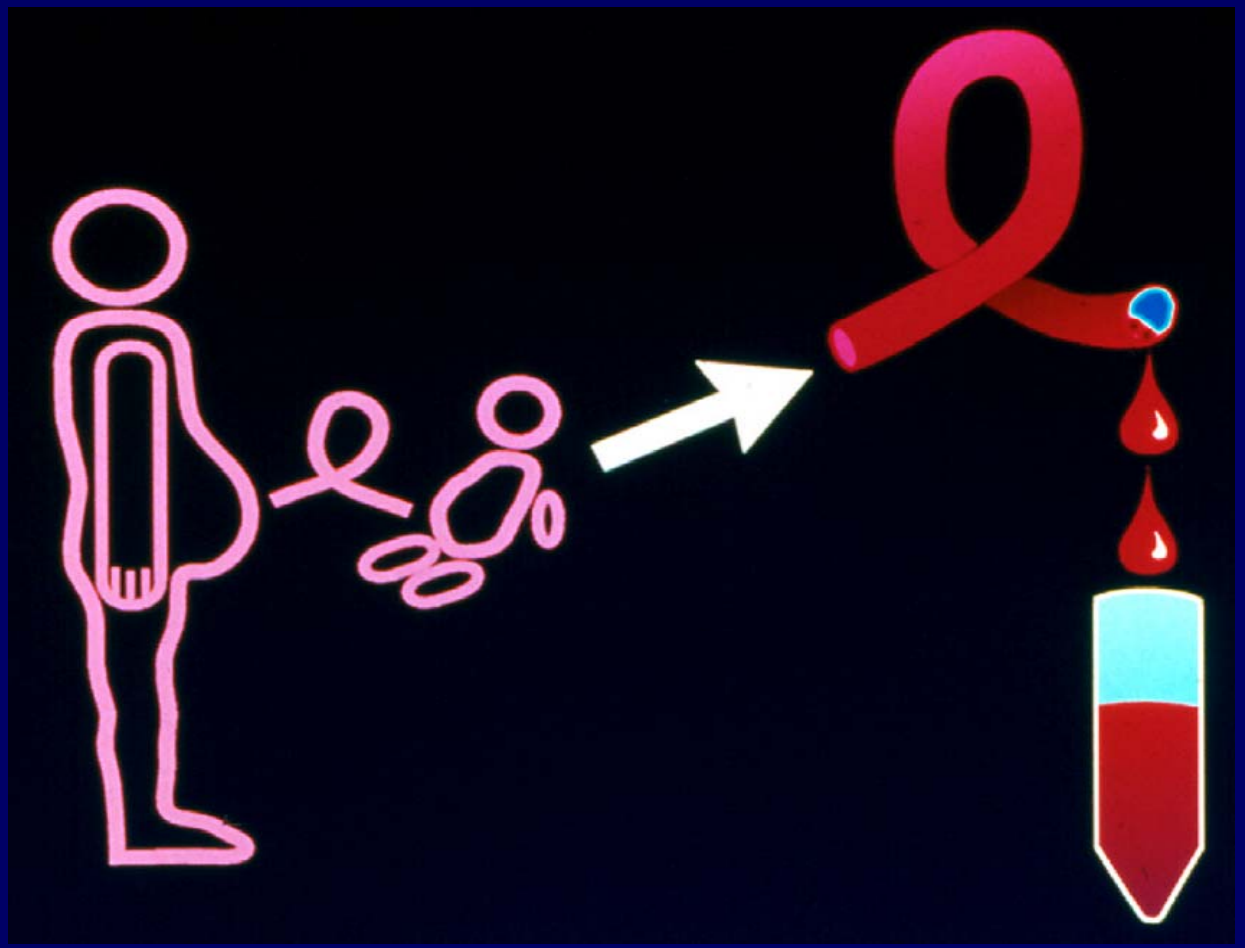
Hypothesis

The best strategy may be to combine adoptive transfer and in vivo expansion followed by HCT

Adoptive Transfer + Transplant

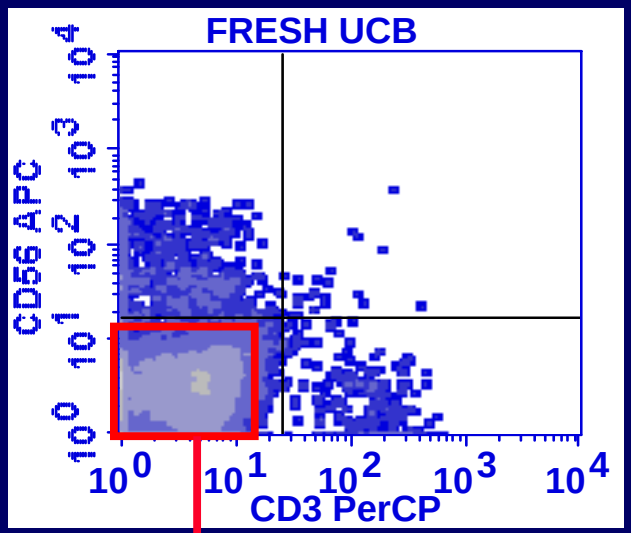
The best of both worlds?

Umbilical Cord Blood

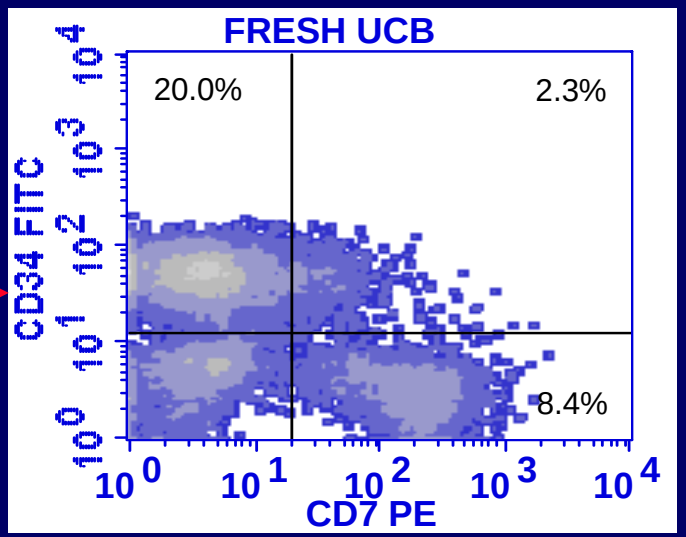


- 100-150 ml cord blood
- Usually discarded
- High concentration of hematopoietic and NK cell progenitors
- Stem cell source for related donor transplant

Cord blood is rich in NK cell precursors



Testing this population clinically



Full Prep Triple UCB strategy: UCB NK + double UCB Transplant for patients with refractory AML

Pablo Rubinstein

New York Blood Center

KIR-L MM if possible

UCB 1

HLA ≤ 2 ag mm TNC
>1.5 x 10^7/kg

THAW

CD3 deplete
IL-2 Overnight
(1000 U/ml)

HLA ≤ 2 ag mm TNC
>1.5 x 10^7/kg

UCB 2

HLA ≤ 2 ag mm

UCB 3

HLA ≤ 2 ag mm TNC
>1.5 x 10^7/kg

THAW

Patient Eligibility

- Age 2-45 years
- Refractory AML

BMBx CY CY FLU FLU FLU TBI BMBx BMBx BMBx

IL-2 x 6 doses for In vivo NK expansion

-25 -19 -18 -17 -16 -15 -14 -13 -12 -1 0 14 28

TIME

CsA (day -1 to 6 months)

MMF (day -1 to day 35 unless GVHD)

Conclusions

- NK cells are important in cancer therapy and transplant.
- Better methods to optimally activate NK cells are still needed for refractory AML patients.
- KIR genotyping may be of value in selecting donors in addition to HLA-typing.

Acknowledgements

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NK PPG working group