Biology of Relapse after Transplantation
Natural Killer Cell Biology and Therapeutic Potential

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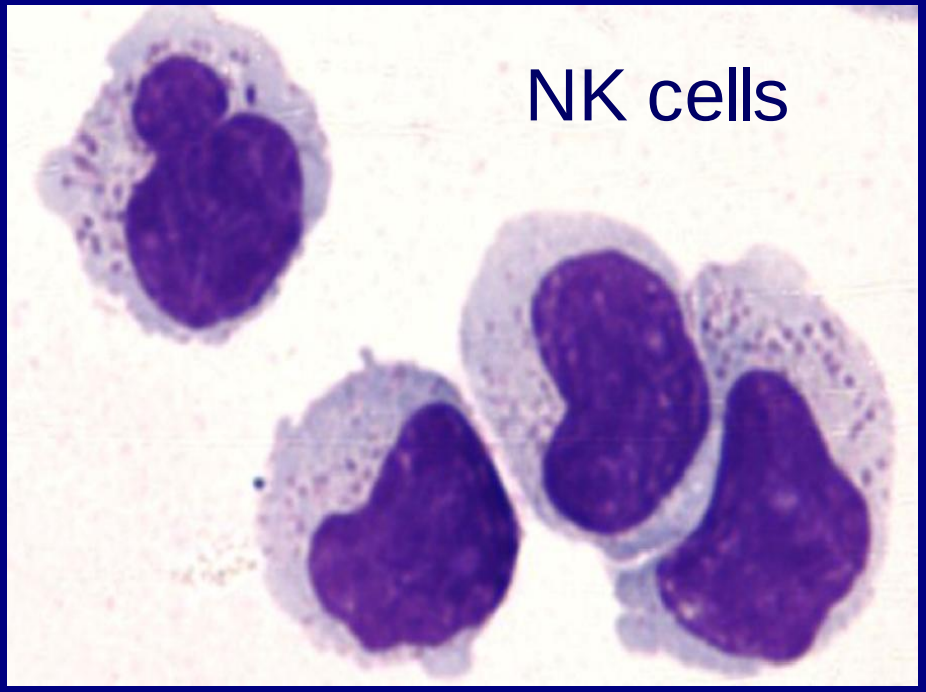
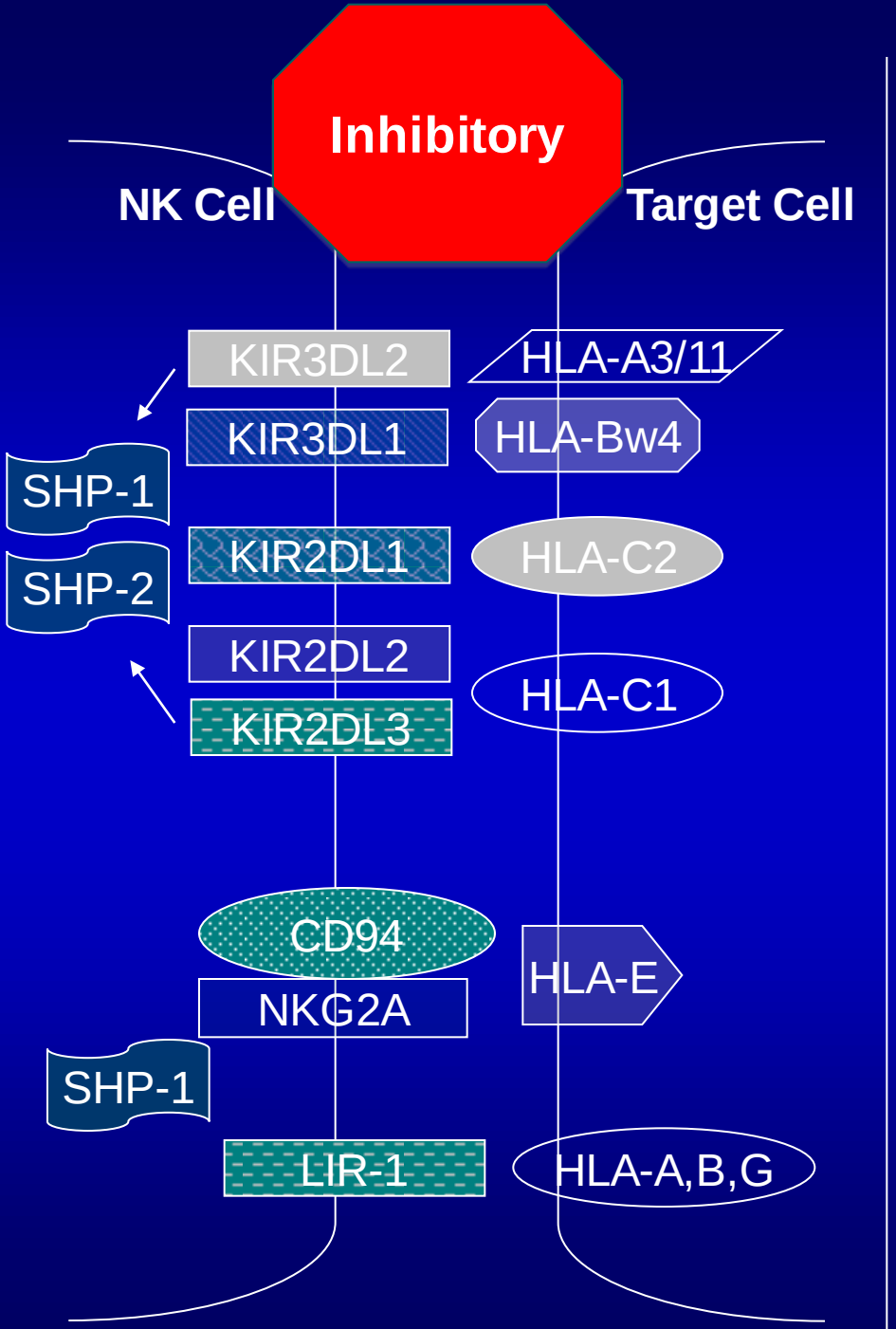
NK cells in health and disease

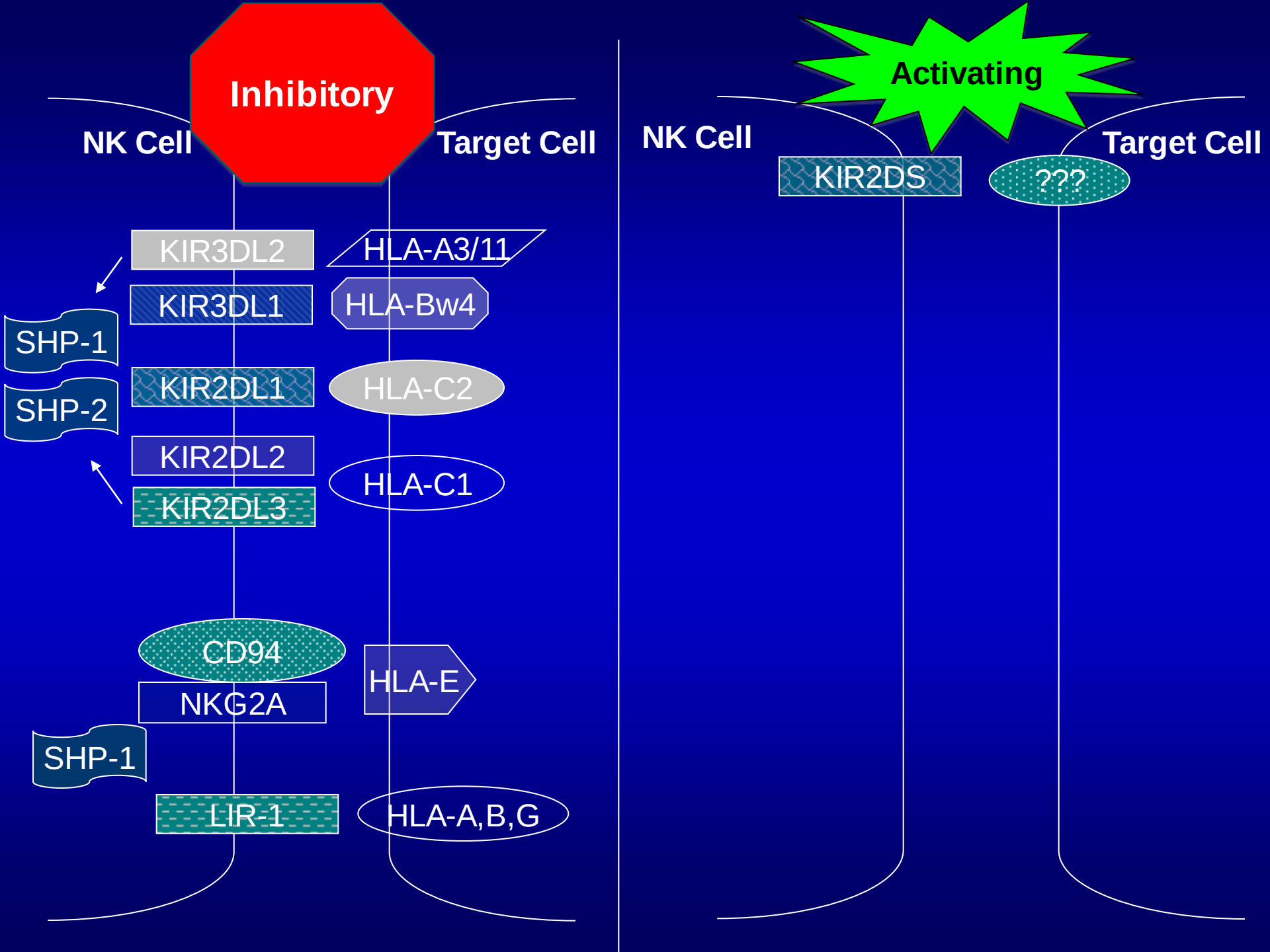


- Cancer treatment and tumor surveillance
- Infection disease control
- Autoimmunity
- Pregnancy (placental angiogenesis)

NK cell functions

- Kill targets
- Produce cytokines
  - Interferon-γ
  - TNF
  - MIP-1β
  - Many others


Inhibitory
NK Cell
Target Cell
KIR3DL2
HLA-A3/11
KIR3DL1
HLA-Bw4
SHP-1
KIR2DL1
HLA-C2
SHP-2
KIR2DL2
HLA-C1
KIR2DL3
CD94
HLA-E
NKG2A
SHP-1
LIR-1
HLA-A,B,G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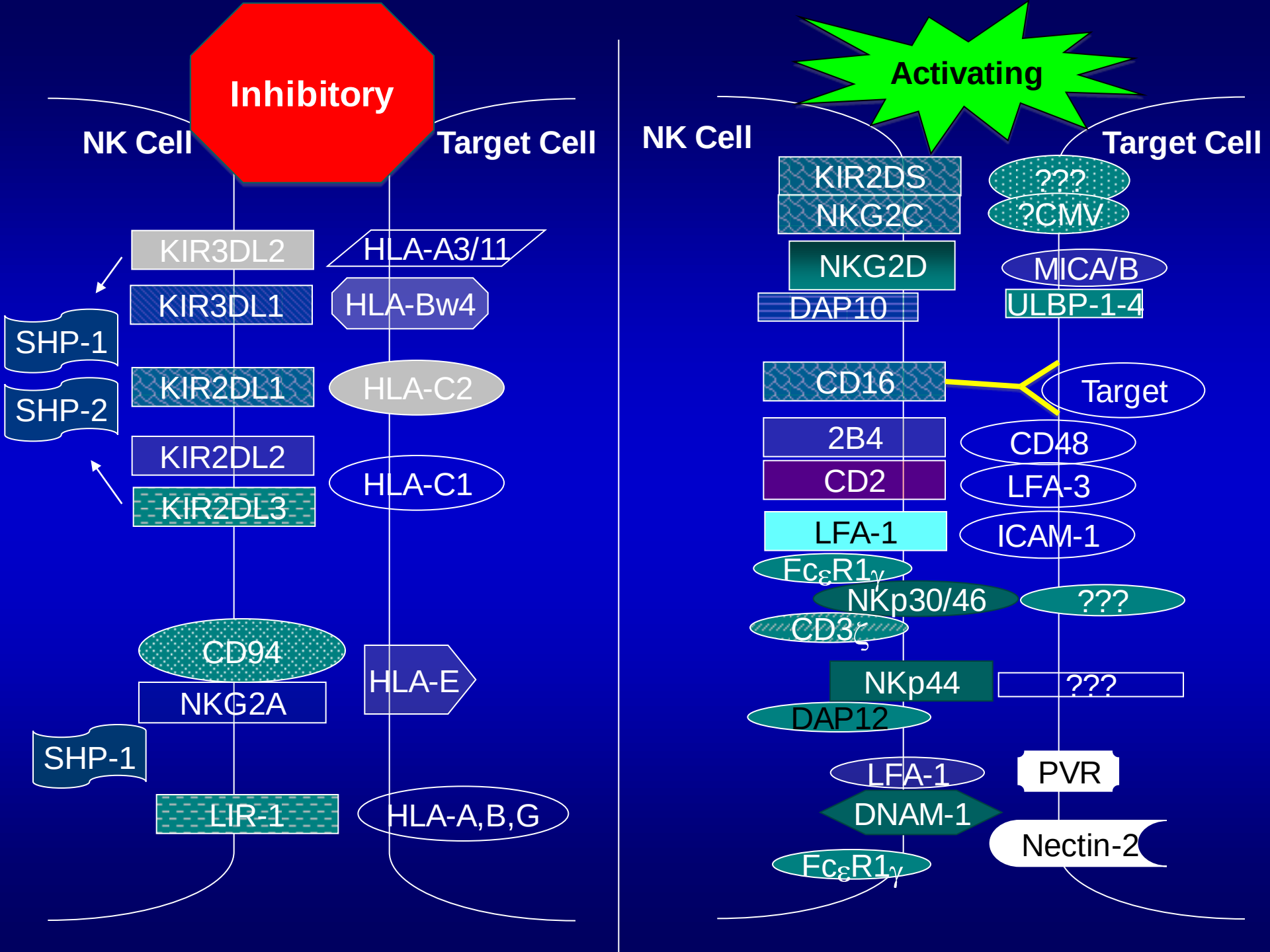
Activating
NK Cell
Target Cell
KIR2DS
???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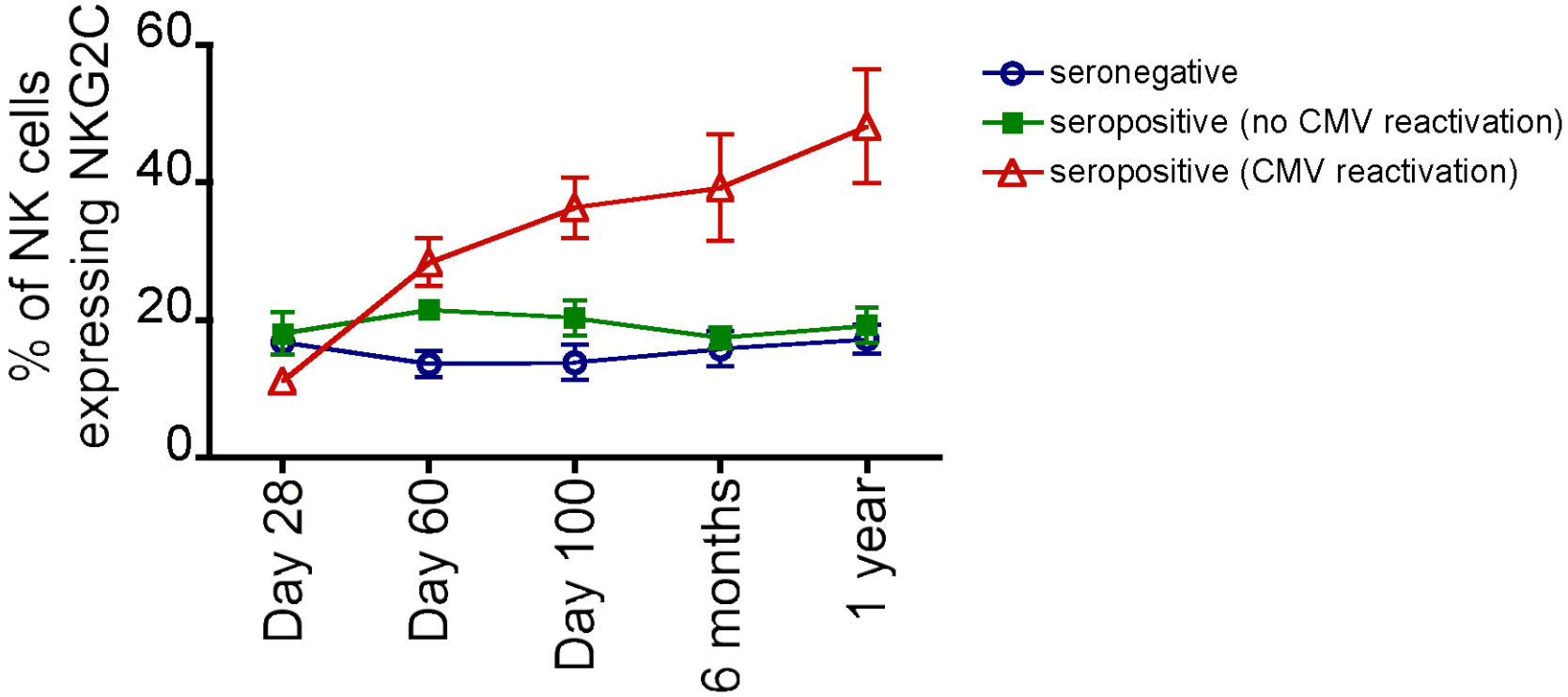
Activating
NK Cell
Target Cell
KIR2DS
???
NKG2C
?CMV
NKG2D
MICA/B
DAP10
ULBP-1-4
CD16
Target
2B4
CD48
CD2
LFA-3
LFA-1
ICAM-1
FcεR1γ
NKp30/46
???
CD3ζ
NKp44
???
DAP12
LFA-1
PVR
DNAM-1
Nectin-2
FcεR1γ

NK Cell Education:
The process by which NK cells acquire function after engagement with "self" inhibitory MHC receptors

NK cells can acquire function by:

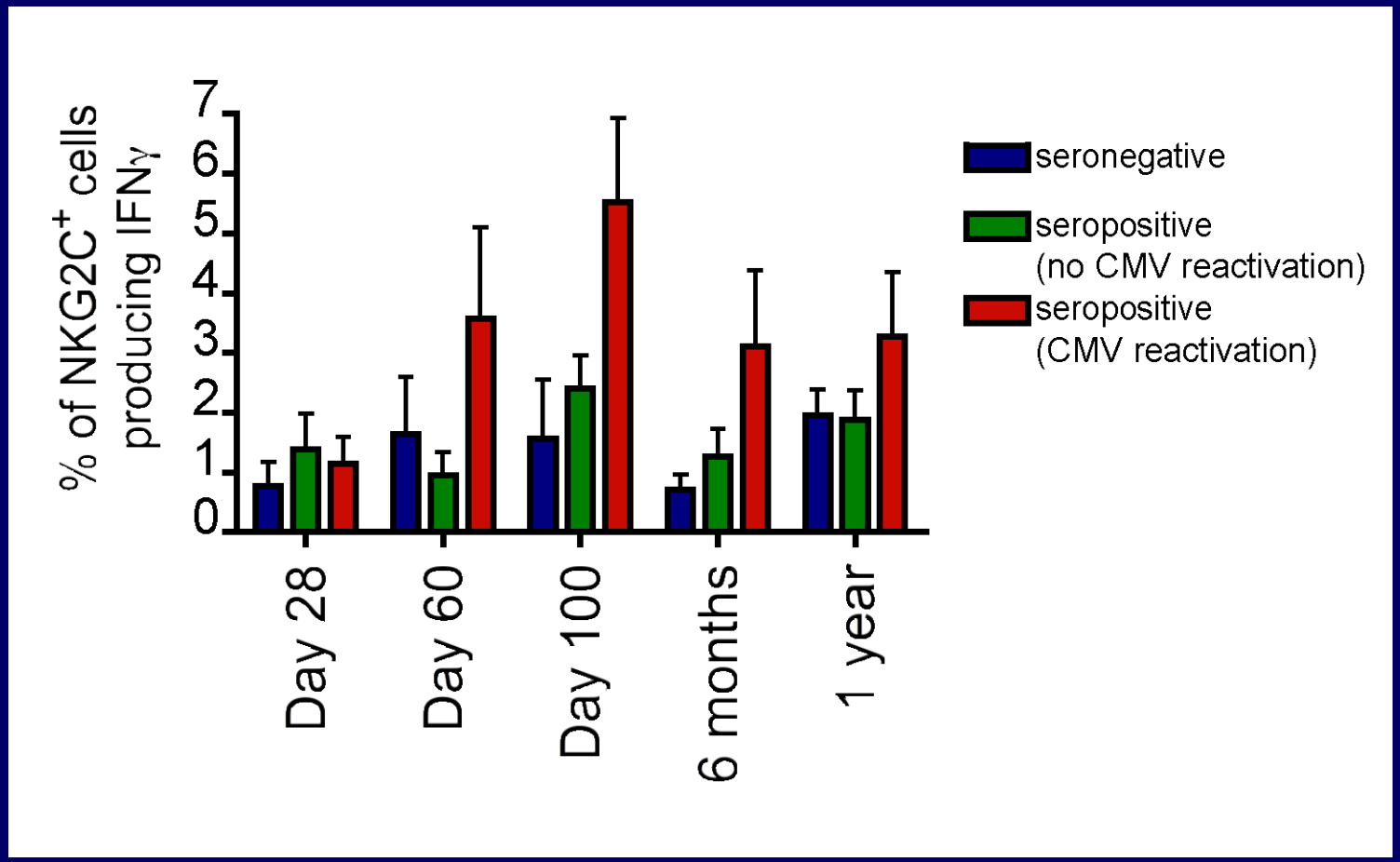
1) **Education**
2) **Cytokine stimulation**
3) **Inflammation (viral infection)**

NKG2C+ NK cells increase following CMV reactivation after UCBT



Foley/Miller et al, Blood 2012 119:2665-2674

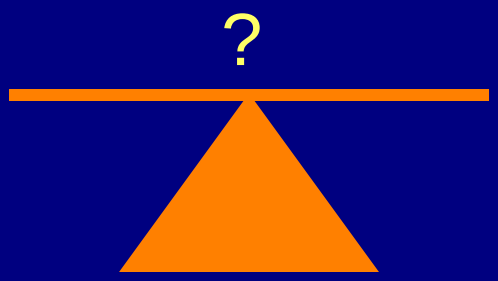
IFNγ production by NKG2C$^+$ NK cells last for a year – these may be memory NK cells



CMV reactivation may promote anti-tumor activity

How can we best exploit NK cells?

Adoptive Transfer



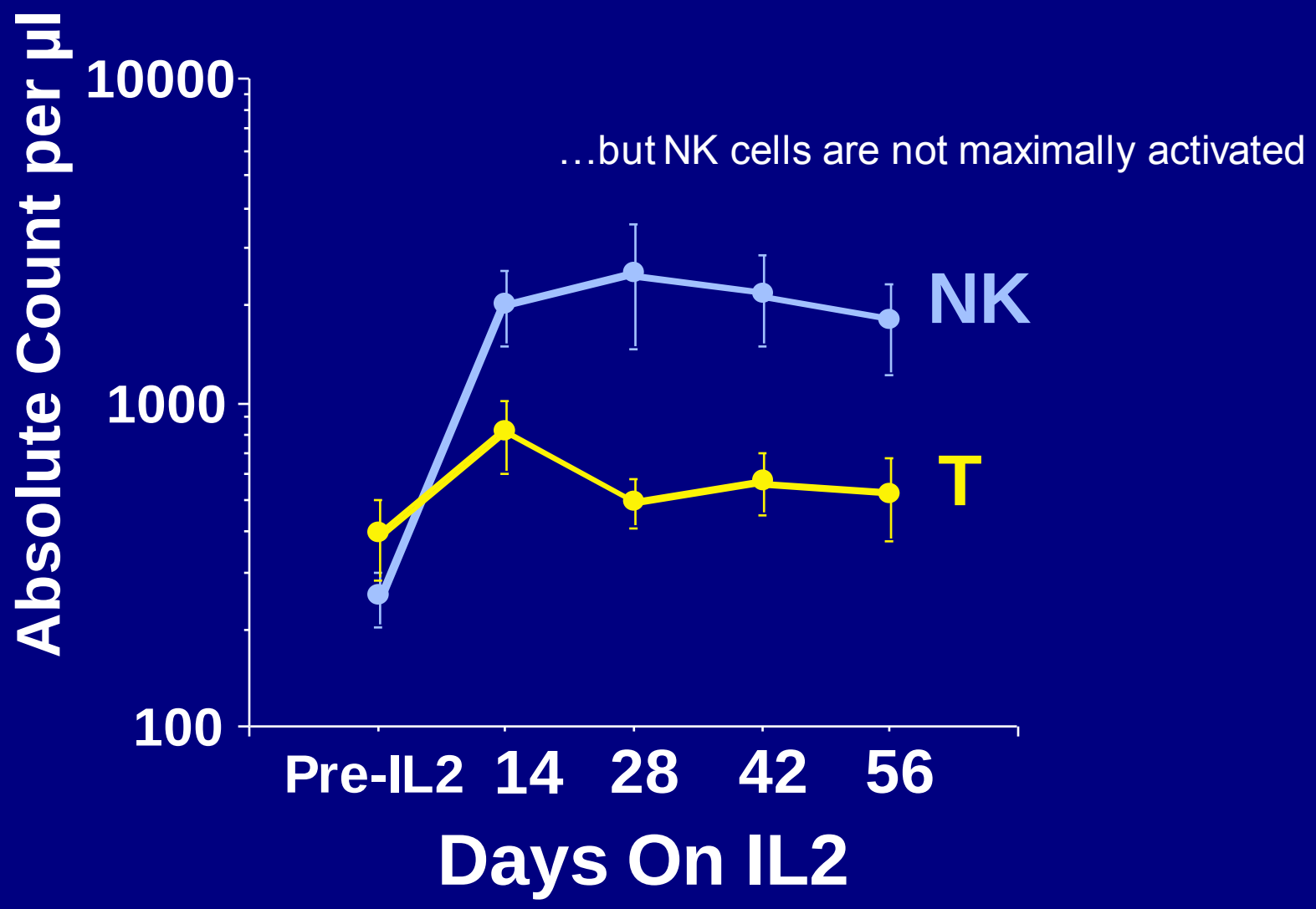
Transplant

Pros and cons

Presumed Functional

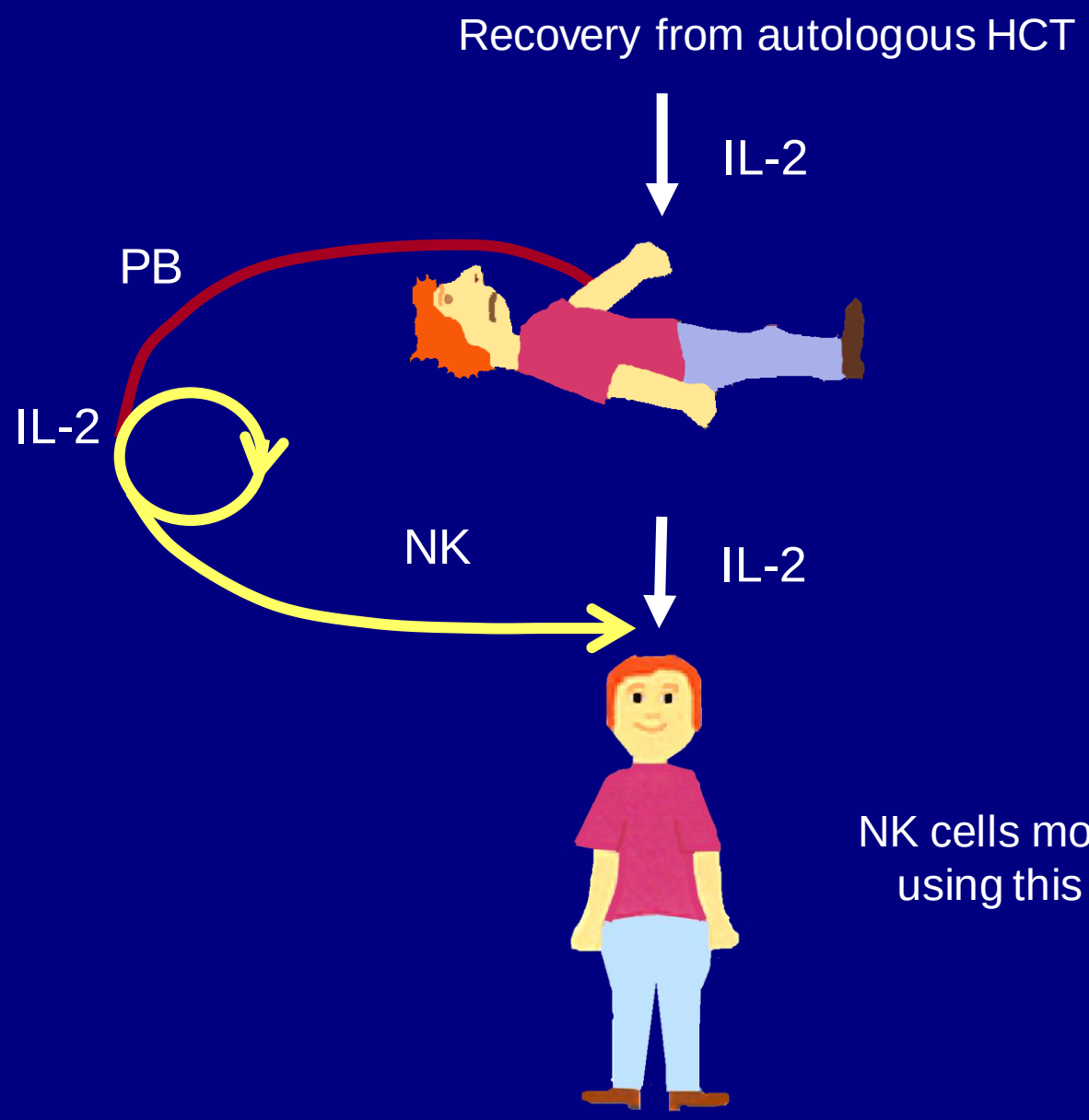
hyporesponsive

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)

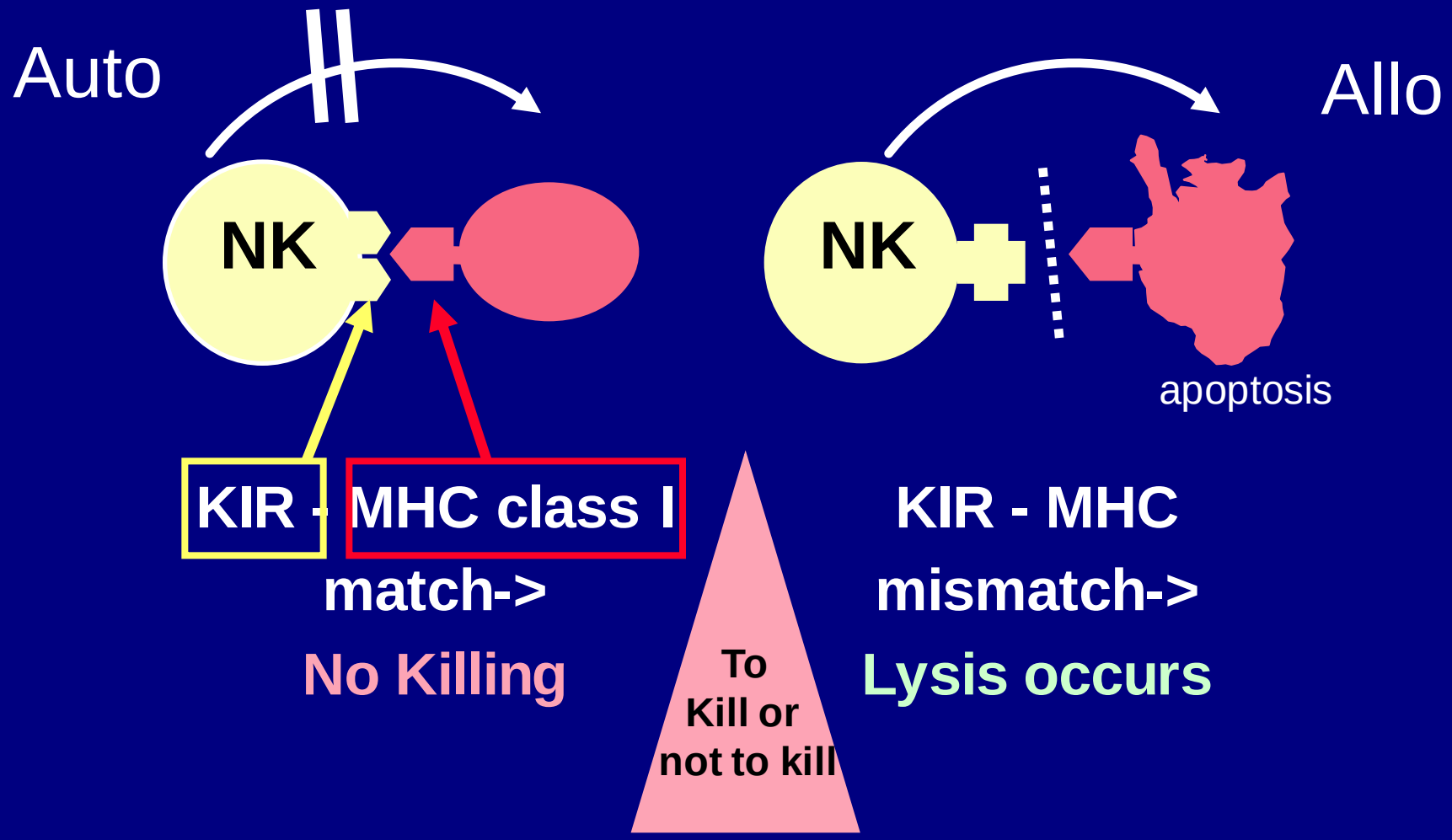
Burns et al, Bone Marrow Transplant, 32:177-186, 2003

Conclusions

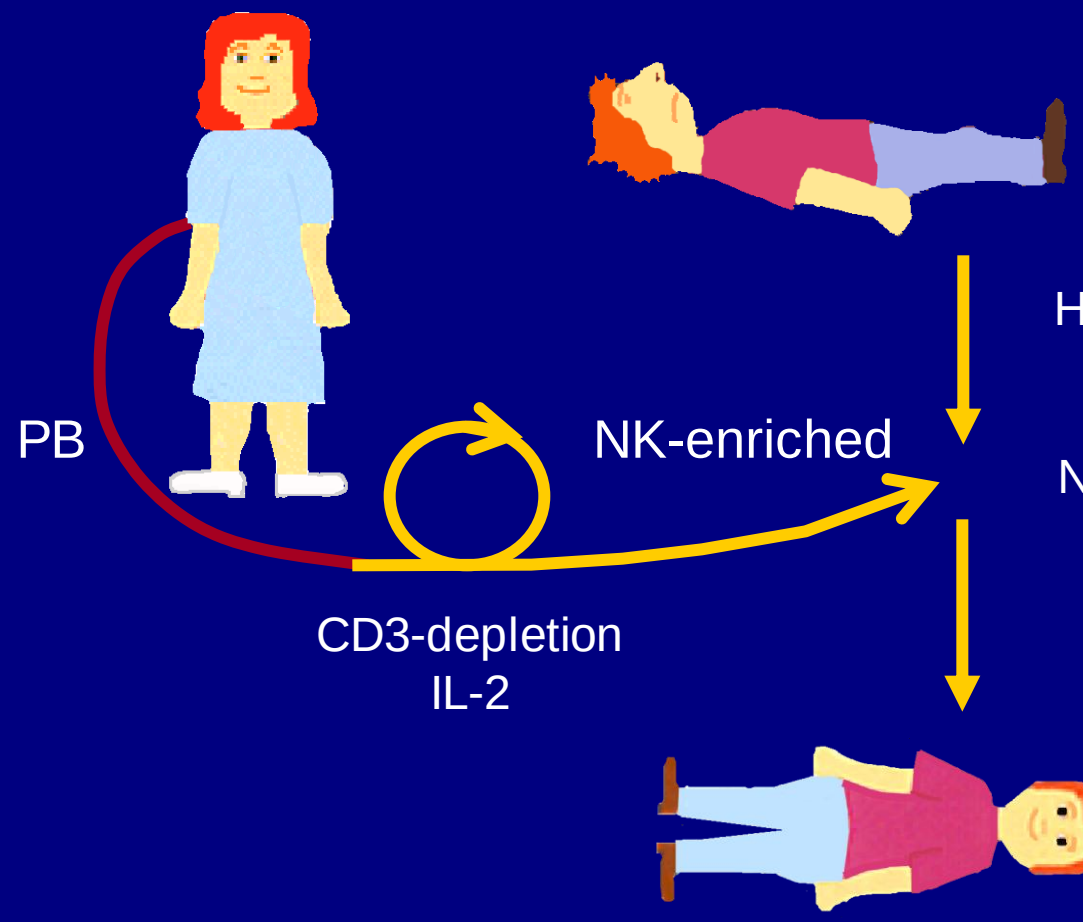
Enhanced activation of NK cells

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



Adoptive Transfer of Human Haploidentical NK Cells



Eligible patients: Poor prognosis with refractory AML

HD Rx	Cy 60 mg/kg x 2 Flu 25 mg/m^2 x 5
NK cells	2-8 x 10^7 MNC/kg
IL-2	10 MU SQ QOD x 6

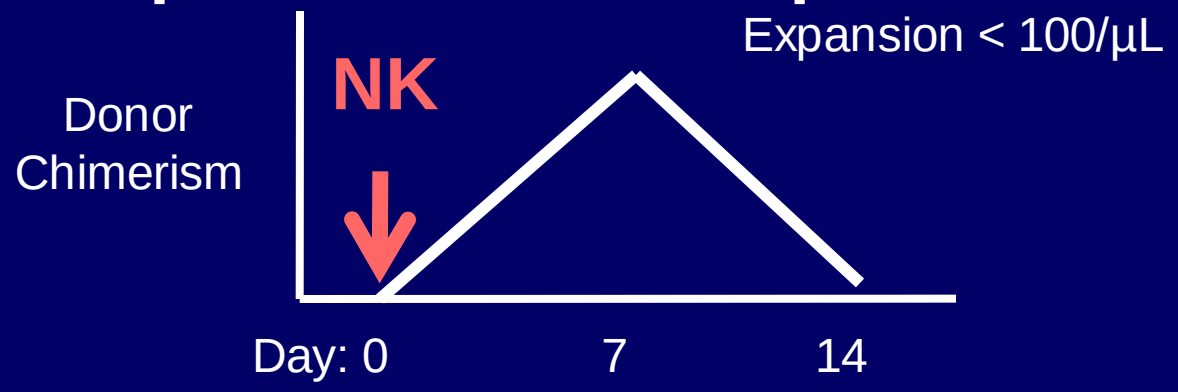
Miller et al, **Blood** 105:3051-3057, 2005

Adoptive Haploidentical NK Cell Therapy for Refractory AML: Cumulative Experience

- Updated clinical follow-up (2003-present)
  - CR in 10 of 32 (31%)
- Limitations
  - Poor in vivo NK expansion (11%)
  - Not curative (4/10 relapsed within 1 year) without subsequent transplant
- Conclusions
  - NK expansion correlates clinical efficacy
  - Lack of NK expansion may be due to immune rejection

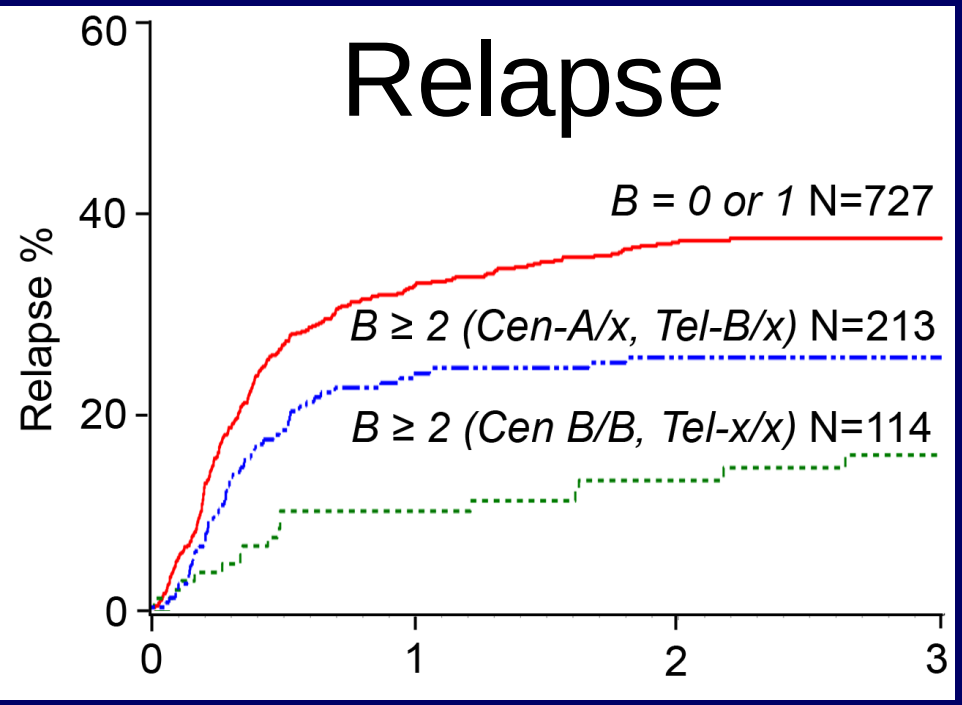
Problems and future directions

- **Some patients do not expand donor NK cells:**

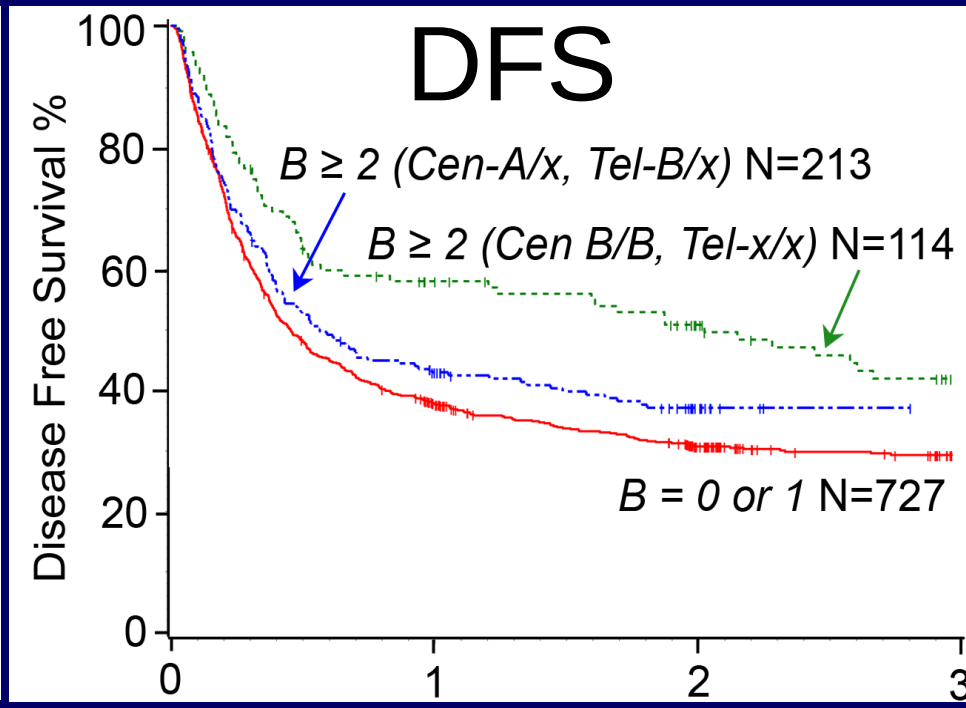


- **Overcoming Suppressive mechanisms**

Donor Factors in HCT: Donors with more *KIR B*-gene content decrease relapse and improve survival



Time since transplantation (years)

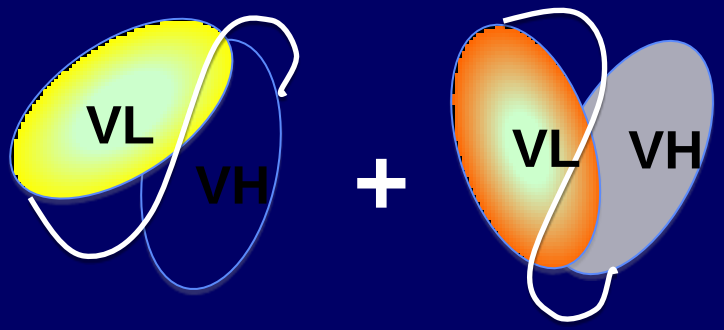


Time since transplantation (years)

Cooley/Miller et al, Blood, *116:2411-2419, 2010*

Bispecific Killer Engagers (BiKEs)

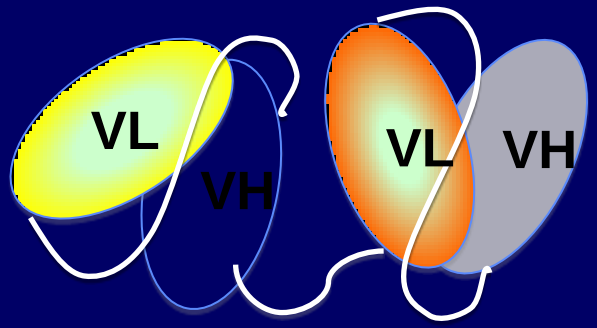
scFV From anti-CD16



scFV From anti-CD33

Dan Vallera

16 x 33 Single Chain Bispecific NK Engager



16 x 33 Enhances NK/Tumor Interaction

P01 (PI: Jeffrey S. Miller)

"NK Cells and their receptors in unrelated donor transplantation"

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