



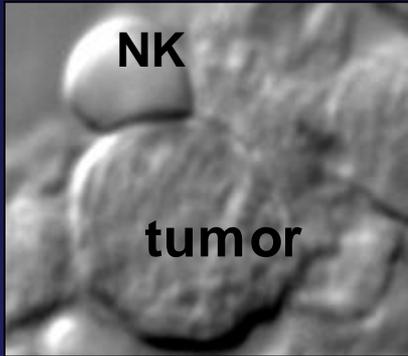
# NK Cell Immunogenetics: Implications for Relapse Risk and Prevention

Katharine Hsu MD PhD

NCI's 2<sup>nd</sup> International Workshop on Post-HCT Relapse

5 November 2012

# TOLERANCE TO SELF



HLA CLASS I

HLA -E



KIR

ILT

CD94/NKG2A

+

-

-

SPONTANEOUS  
CYTOTOXICITY



PVR



DNAM

+

NKG2D



ADCC

CD16



Ig-target cell  
immune complex

CD137



NK Cell

NKp-46



p-30



p-44

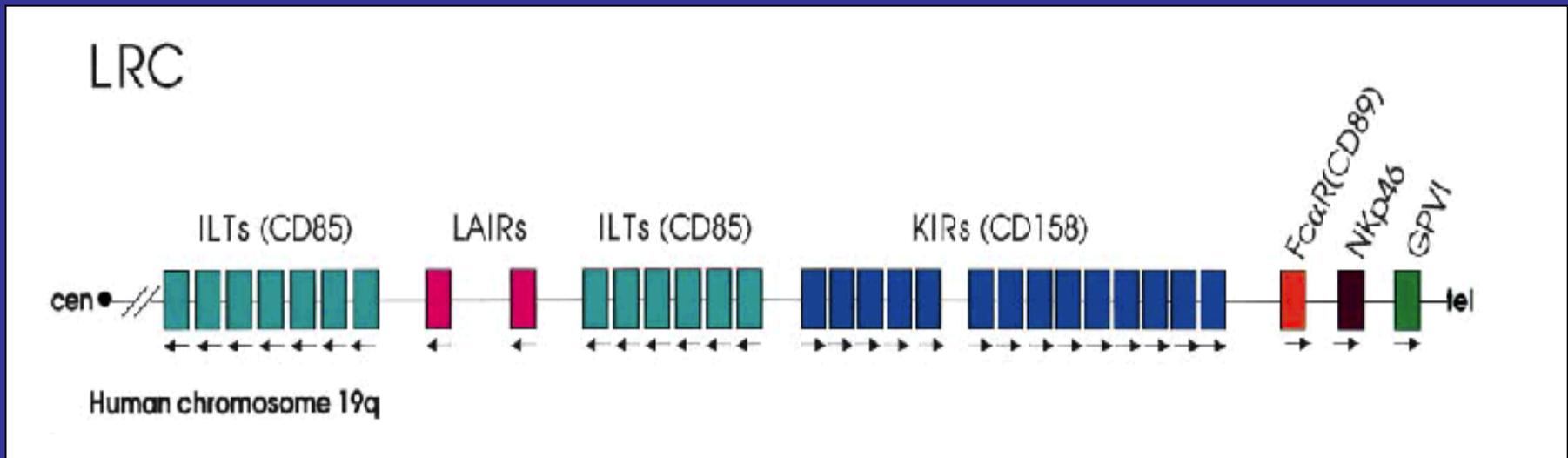


NATURAL CYTOTOXICITY RECEPTORS

MICA/B/UL16-BP  
Expressed on tumors  
of epithelial origin



# KIR Genomic Region

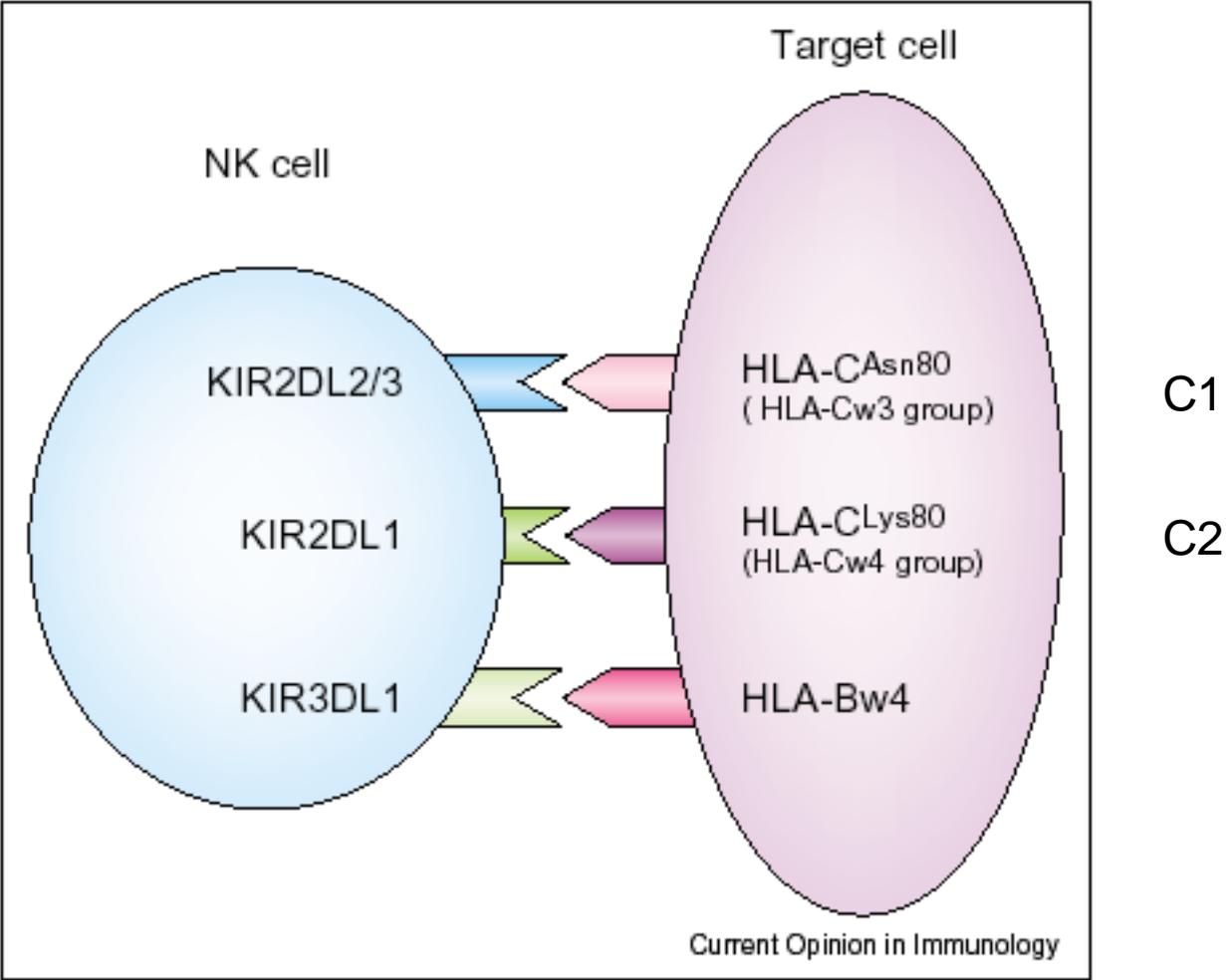


# KIR Genotypes

Genotype	3DL3	2DS2	2DL2	2DL3	2DP1	2DL1	3DP1	3DP1v	2DL4	3DL1	3DS1	2DL5	2DS3	2DS5	2DS1	2DS4	1D	3DL2	No.	(%) n=85
A																			1	1.2
B																			1	1.2
C																			1	1.2
D																			1	1.2
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O																			1	1.2
P																			1	1.2
Q																			1	1.2
R																			1	1.2
S																			1	1.2
T																			1	1.2
U																			1	1.2
V																			1	1.2
W																			1	1.2
X																			1	1.2
Y																			1	1.2
Z																			1	1.2
AA																			1	1.2
AB																			2	2.4
AC																			1	1.2
AD																			1	1.2
AE																			2	2.4
AF																			9	10.6
AG																			14	16.5
AH																			4	4.7
AI																			9	10.6
AJ																			1	1.2
	3DL3	2DS2	2DL2	2DL3	2DP1	2DL1	3DP1	3DP1v	2DL4	3DL1	3DS1	2DL5	2DS3	2DS5	2DS1	2DS4	1D	3DL2		

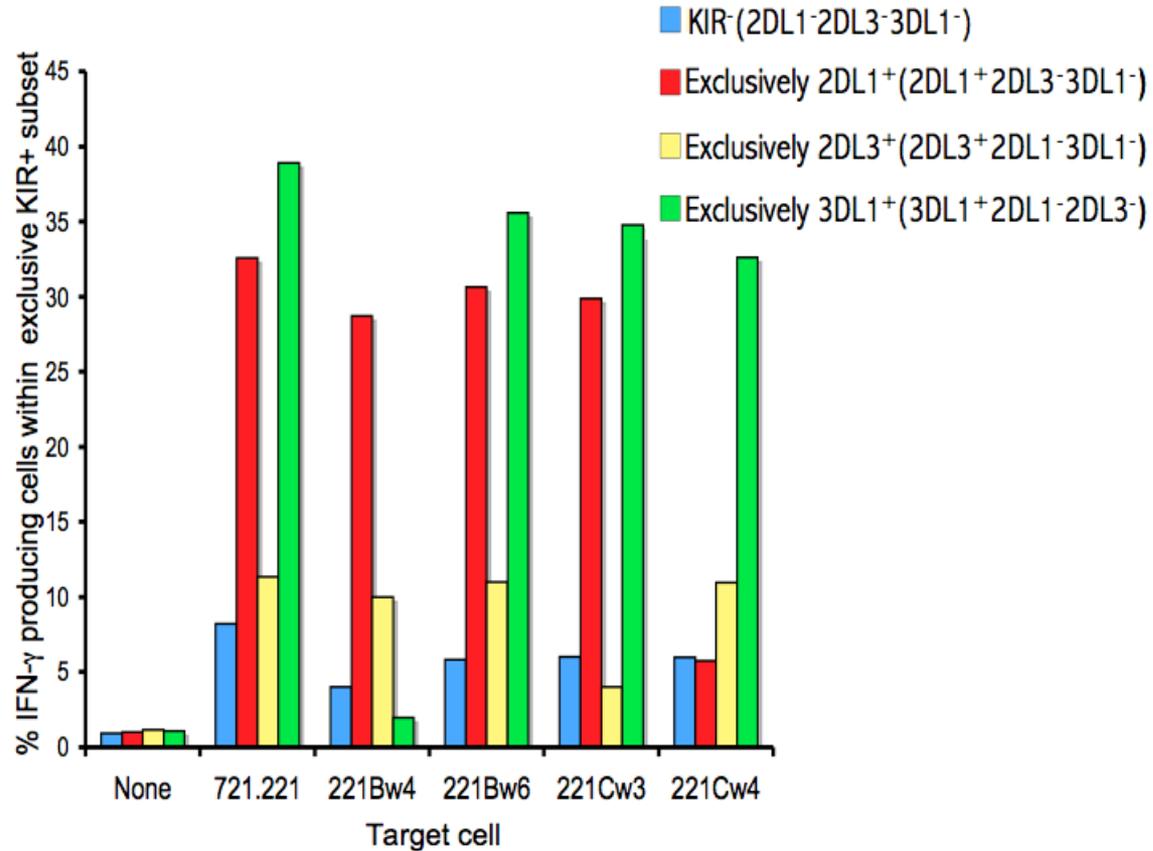
36 unique genotypes are identified by gene content in a Caucasian population (n=85).

# Inhibitory KIR recognize class I ligands



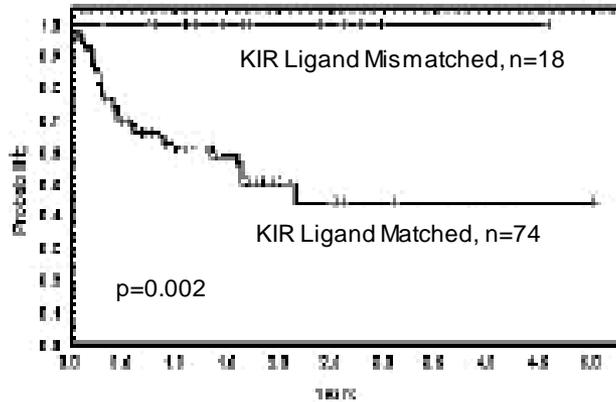
# NK Licensing in an HLA-C2/C2, Bw4/Bw6 Donor

C2/C2, Bw4/Bw6 Donor  
KIR2DL1, 3DL1 S-KIR

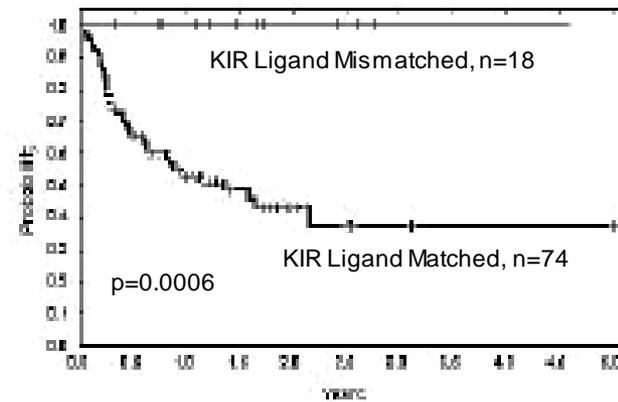


# KIR ligand incompatibility in MM-HCT

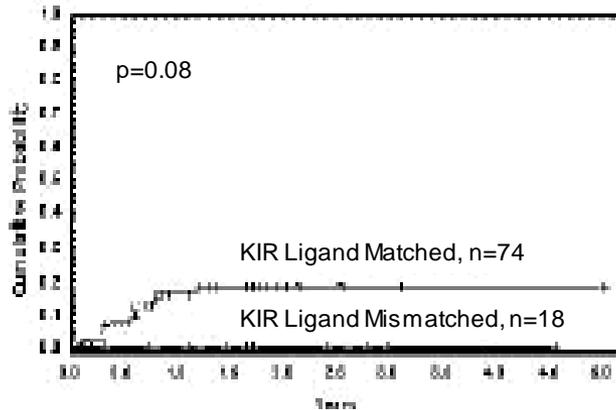
a) Overall Survival



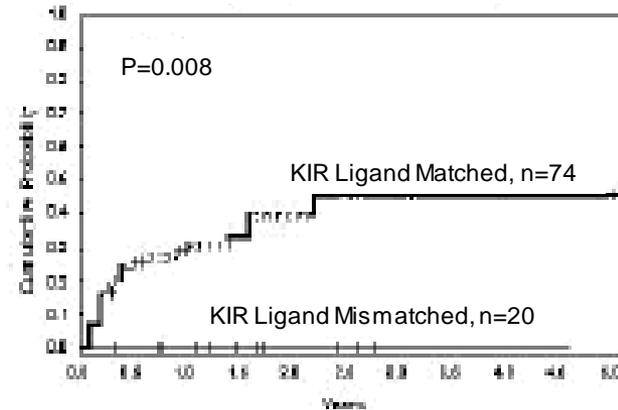
b) Disease Free Survival



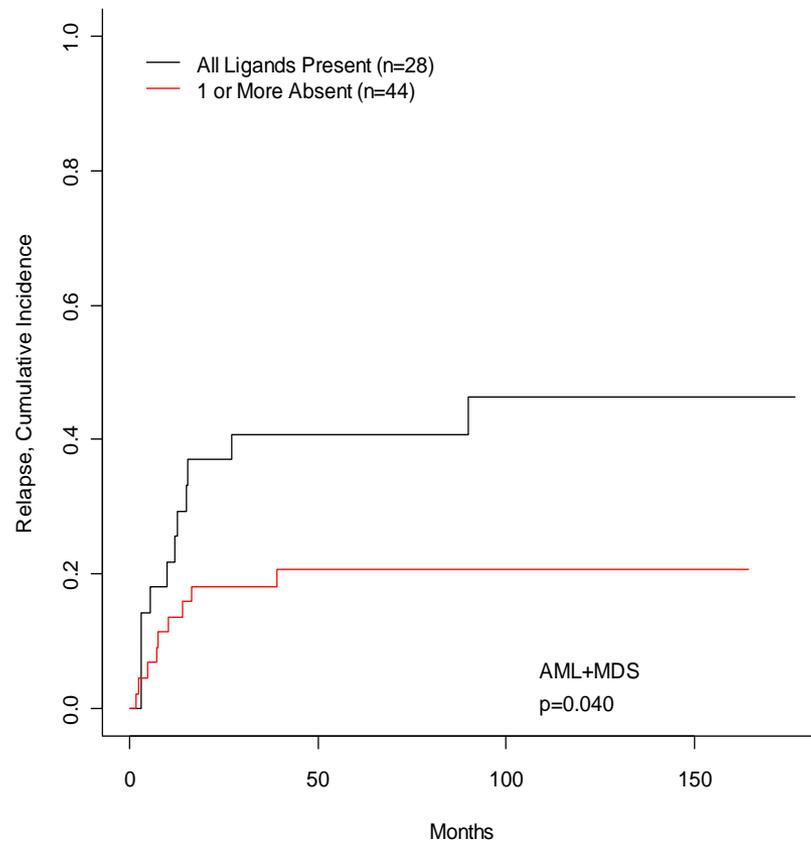
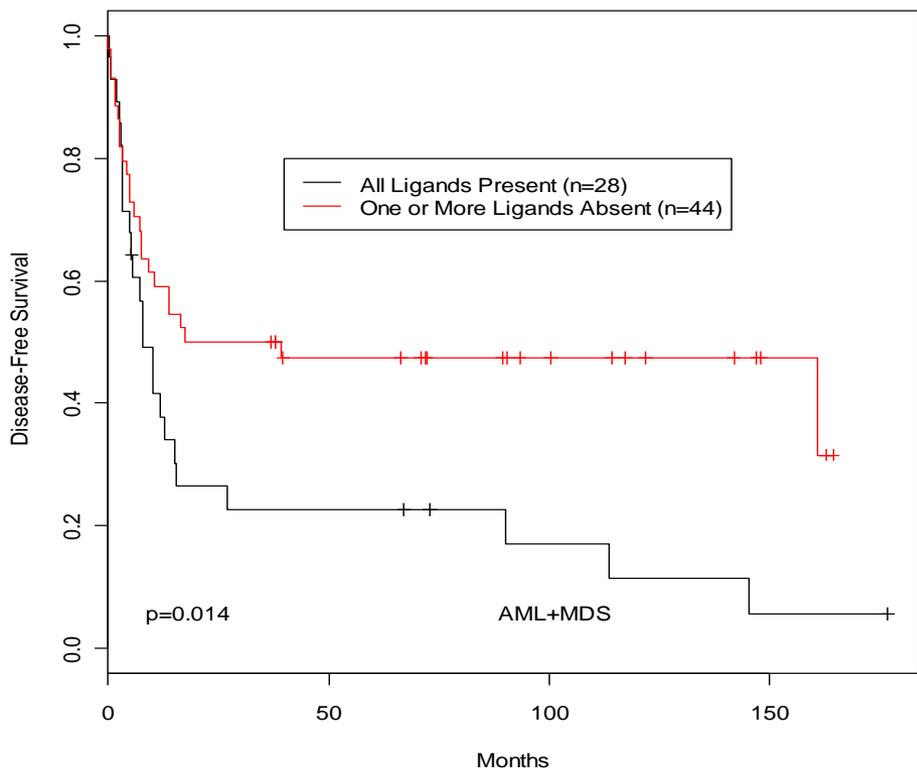
c) Relapse Incidence



d) Transplant-Related Mortality

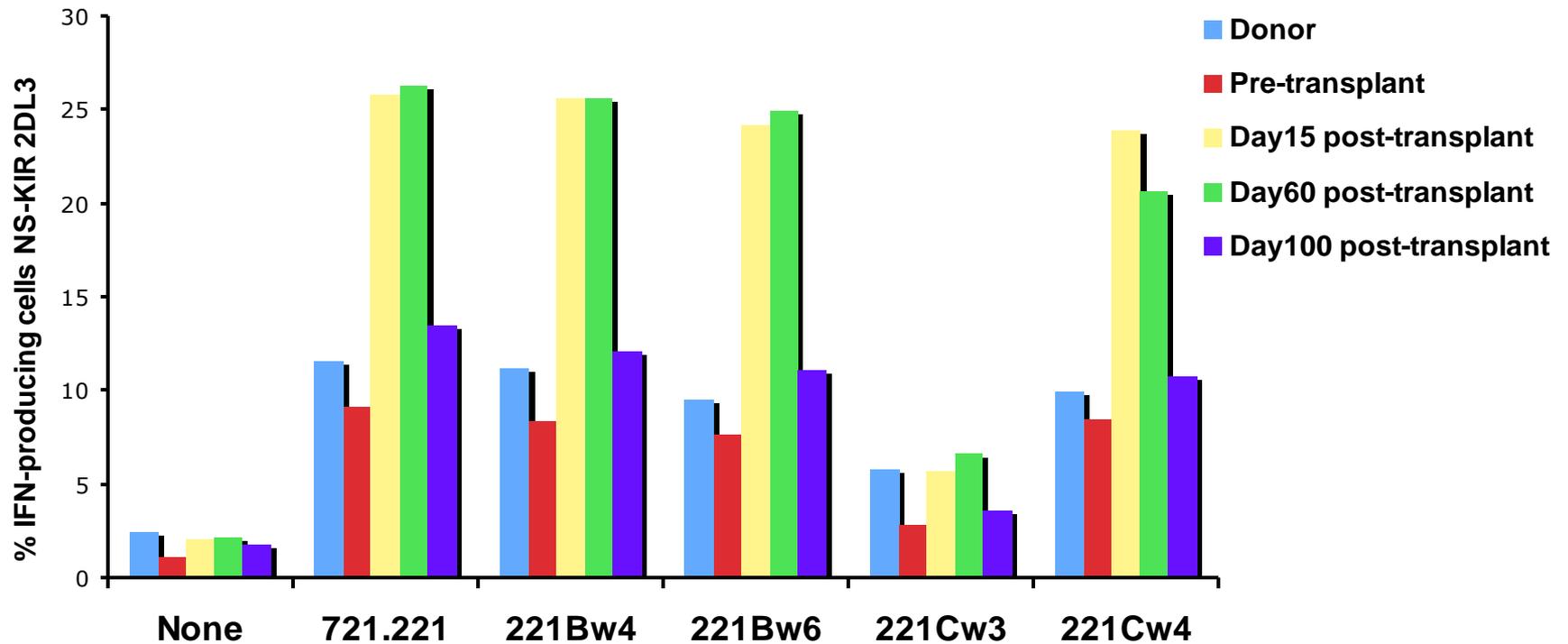


# Missing KIR Ligand Effect in HLA-Identical TCD-HCT for AML/MDS



# NS-KIR expressing NK cells display functional activity early post-HSCT, behaving according to missing ligand

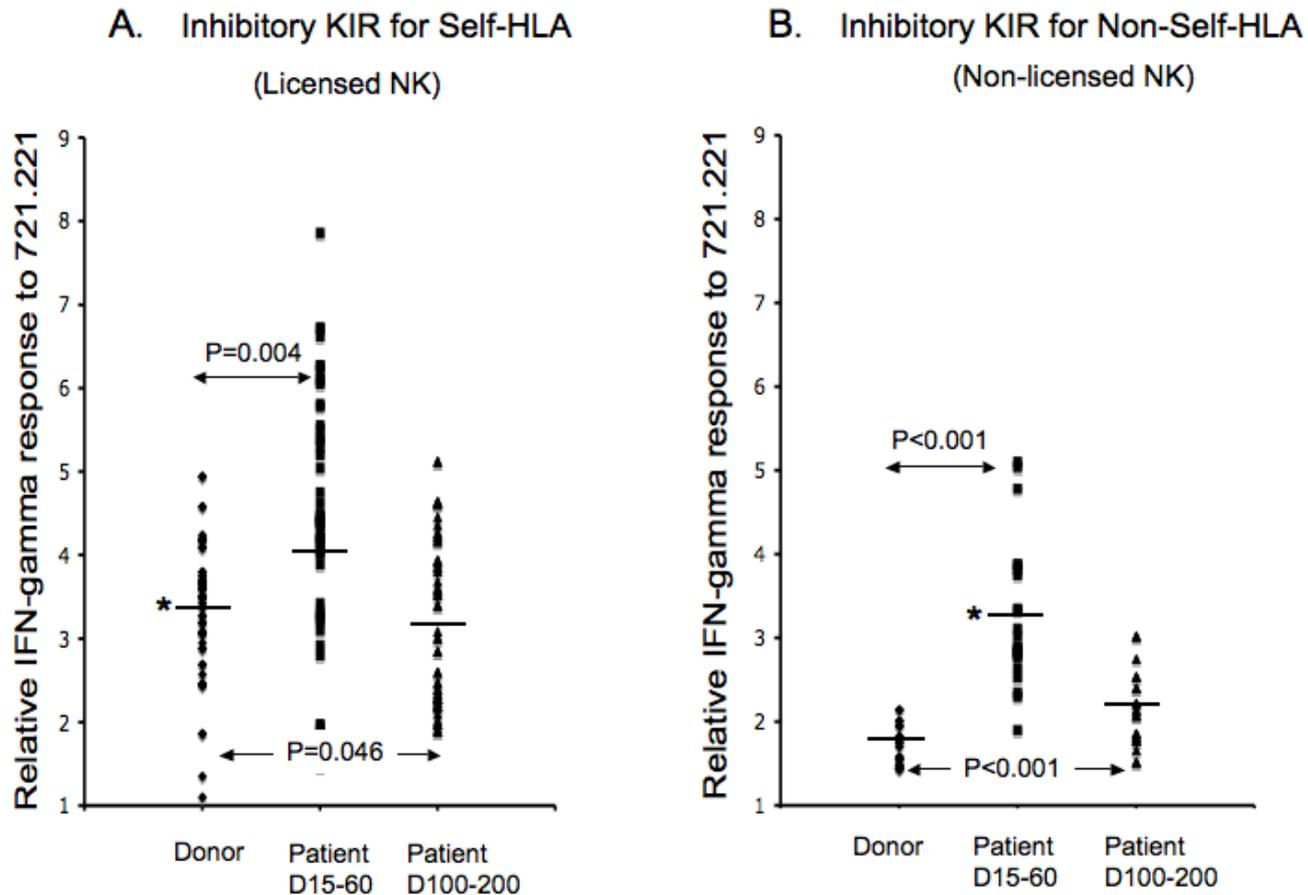
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C2/C2 donor and patient

# NK cells expressing KIR for non-self display functional competence early post-TCD HSCT

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# Neuroblastoma and NK

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Most frequently diagnosed cancer in infants

Susceptible to NK-mediated lysis in vitro and in vivo

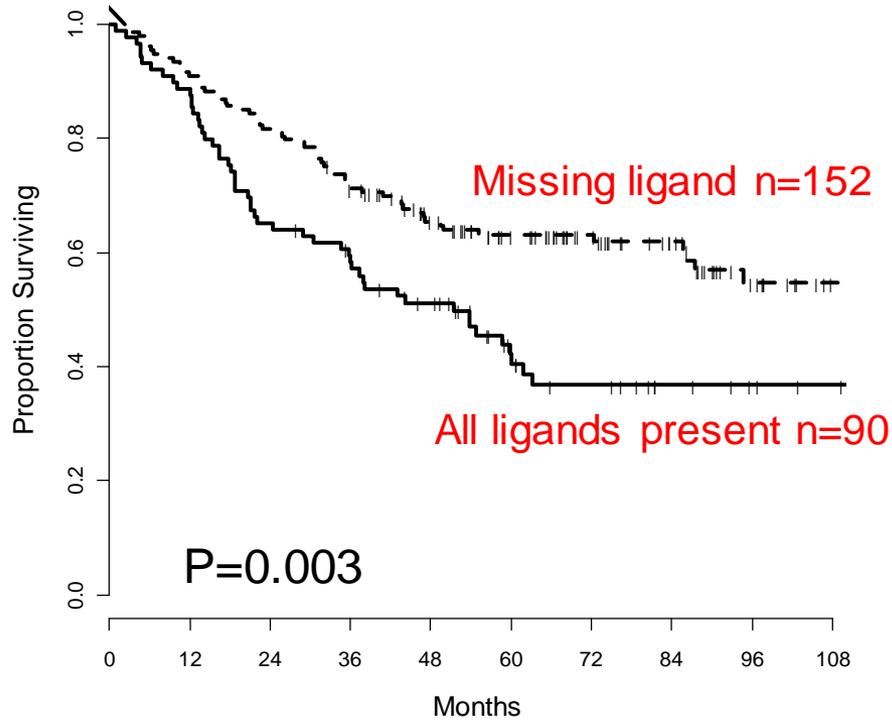
Key roles played by PVR/DNAM-1

B7-H3 permits evasion from NK cell cytotoxicity

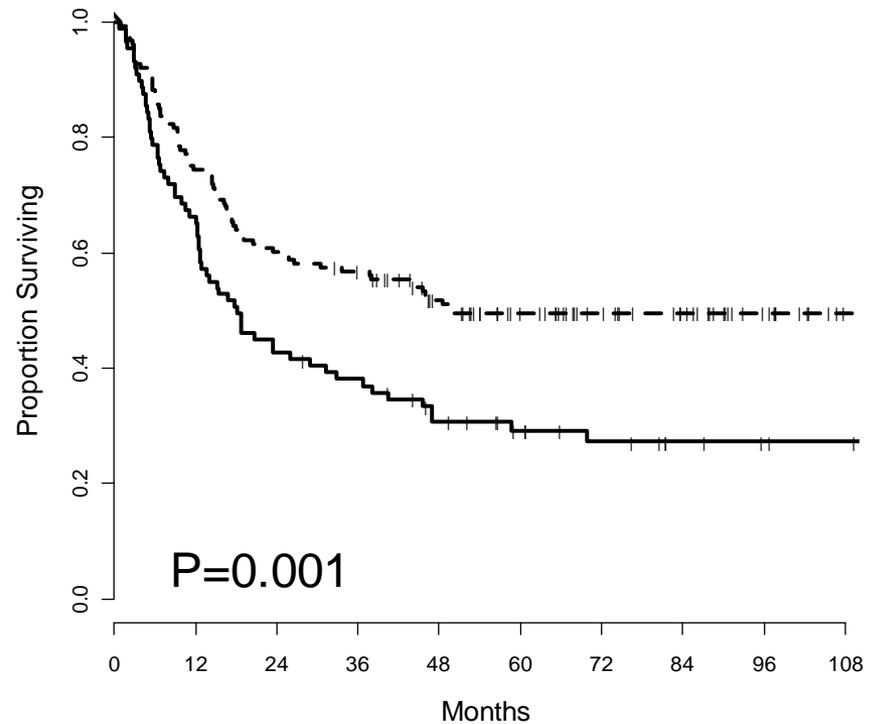
Expresses high levels of disialoganglioside GD2

# Lack of KIR ligand is associated with higher survival in patients treated with anti-GD2 moAb

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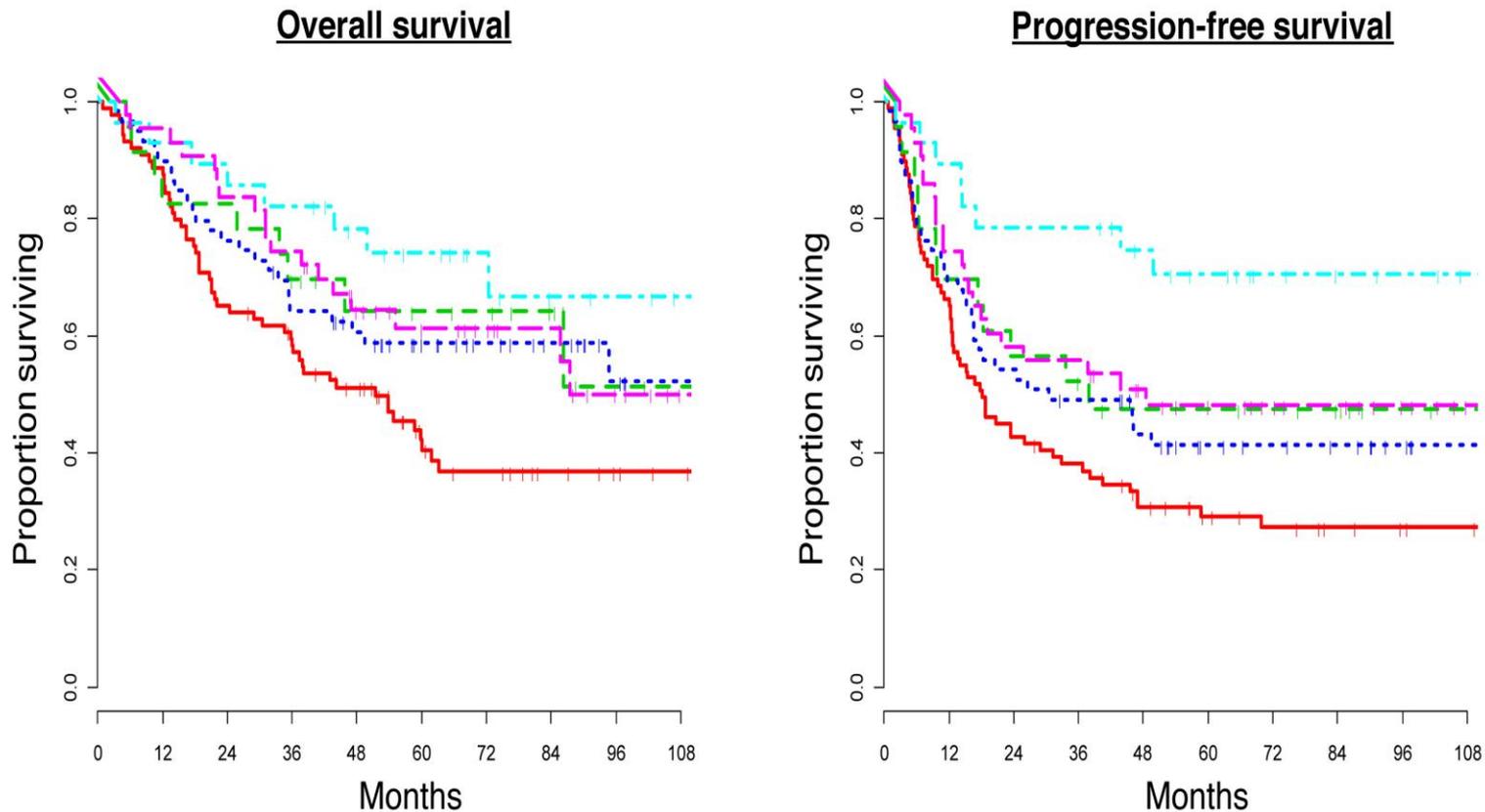


**Overall Survival**



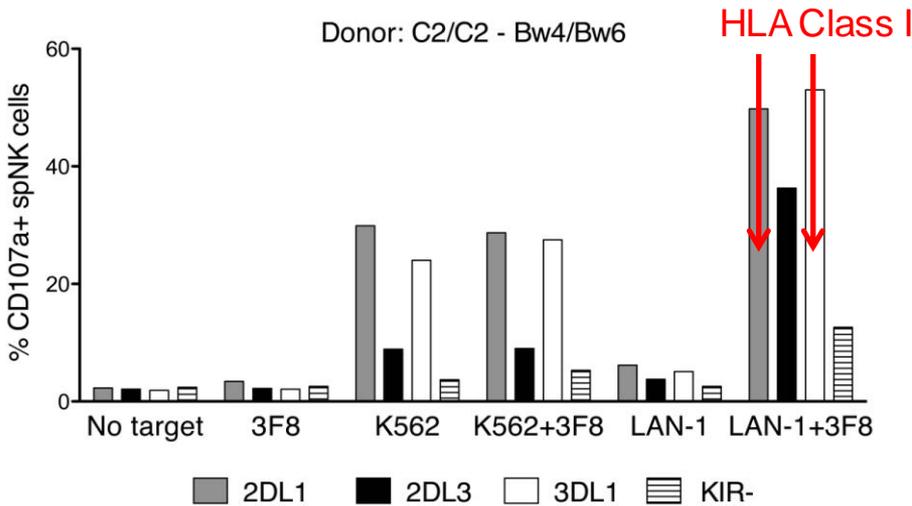
**Progression-Free Survival**

# Lack of *any* KIR ligand is associated with higher survival in patients treated with anti-GD2 moAb



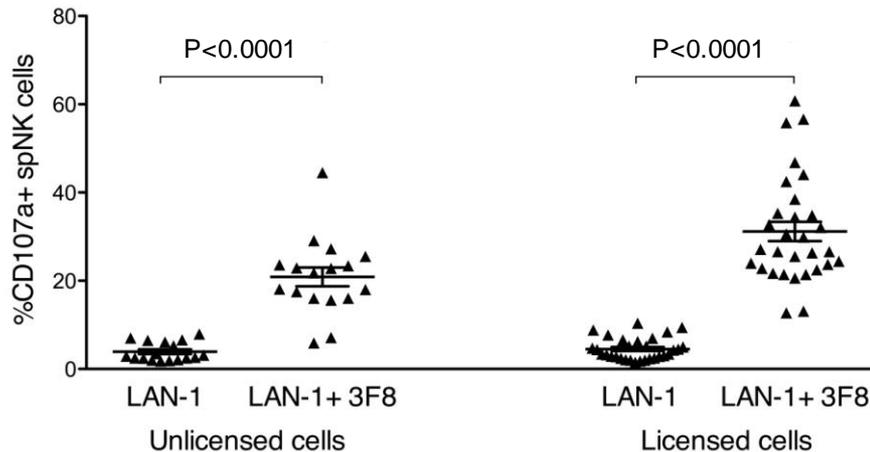
- All KIR ligands present ( $n=89$ )
- - Missing HLA-C1 for KIR2DL2/3 ( $n=23$ )
- ... Missing HLA-C2 for KIR2DL1 ( $n=59$ )
- . - . Missing HLA-Bw4 for KIR3DL1 ( $n=28$ )
- . - . Missing 2 ligands ( $n=43$ )

# Unlicensed and licensed NK cells are activated by 3F8

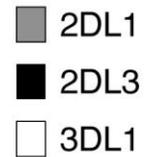
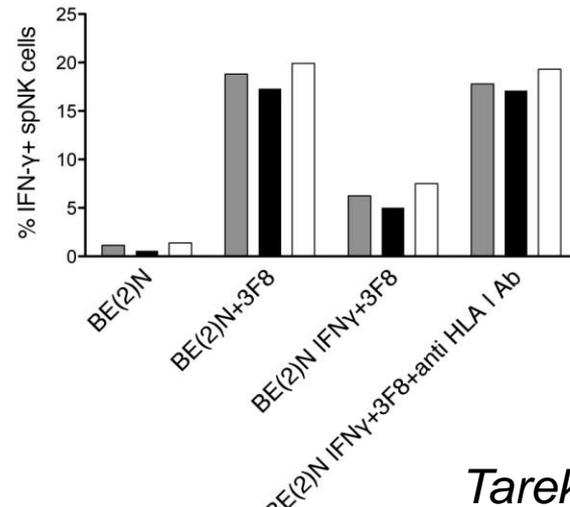
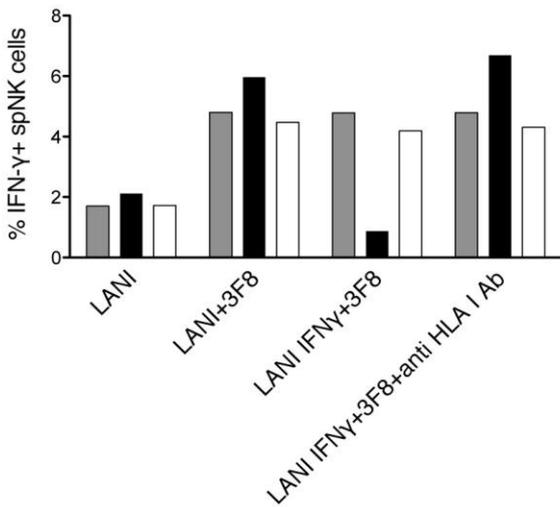
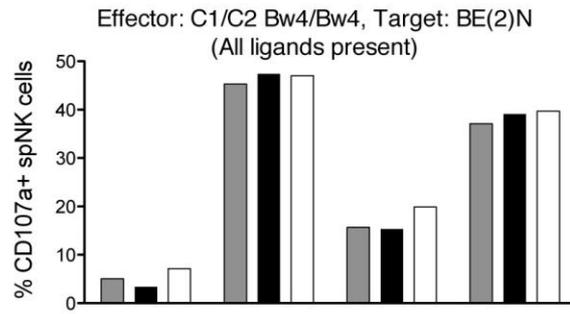
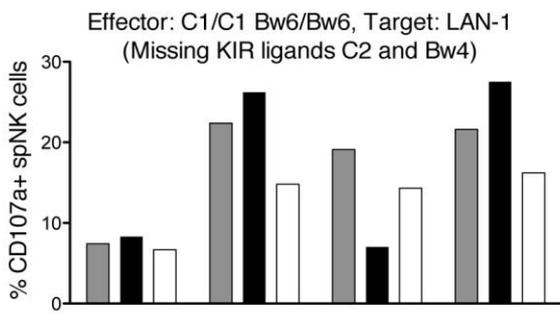
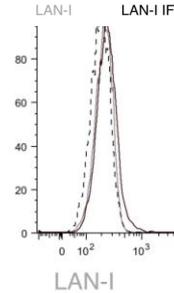
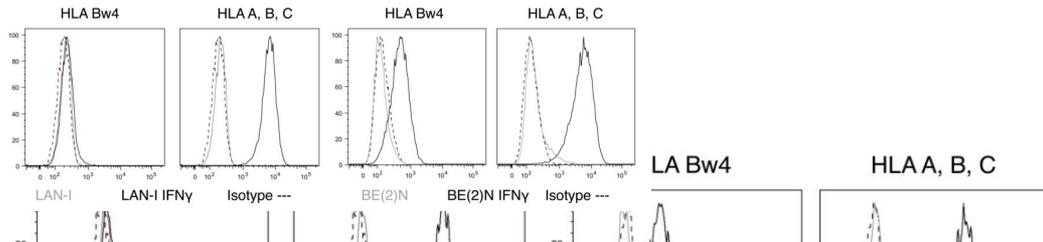


HLA class I molecules are upregulated on neuroblastoma cells by:

- Chemotherapeutic agents
- Retinoic acid
- Anti-GD2 antibodies

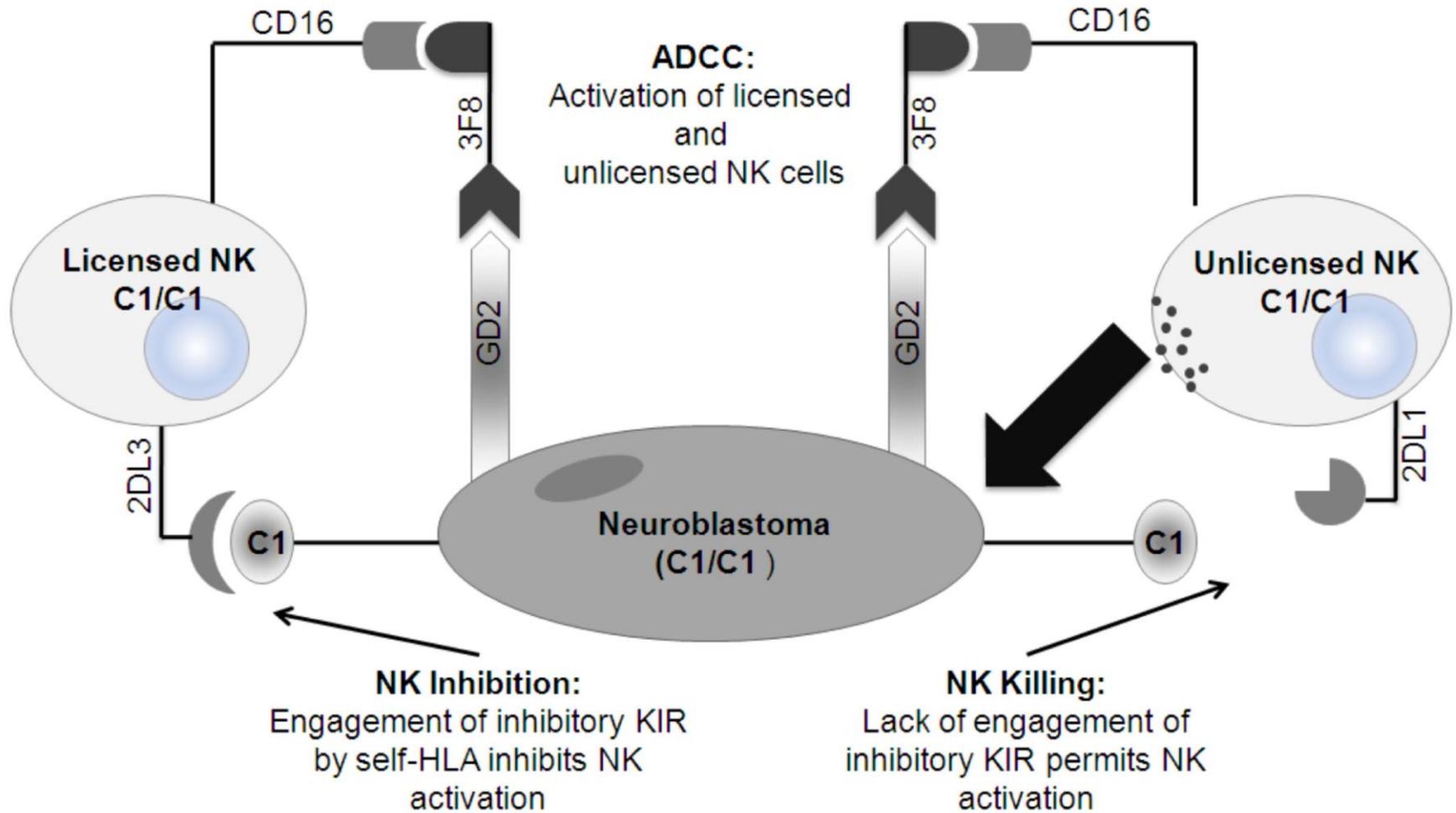


# HLA class I on tumor cells inhibits licensed NK activity



# Class I expression on target cells inhibits licensed NK

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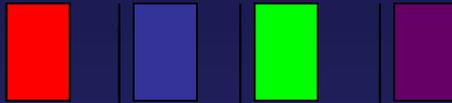
# Newest approaches in myeloma treatment all enhance autologous NK activity

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- **Bortezomib**: reduces class I on target
- **Lenalidomide**: upregulates NK activity
- **Anti-KIR antibody**: disinhibits NK
- **Anti-CS1 antibody**: NK-mediated ADCC
- **Anti-PD1 antibody**: disinhibits NK activity
- **Anti-CD137 antibody**: enhances ADCC

# TOLERANCE TO SELF

## HLA CLASS I



CD94/NKG2A

KIR

ILT

PD-1

## ADCC

CD16

Ig-target cell  
immune complex

CD137

NK Cell

## SPONTANEOUS CYTOTOXICITY



PVR



DNAM



NKG2D

NKp-46



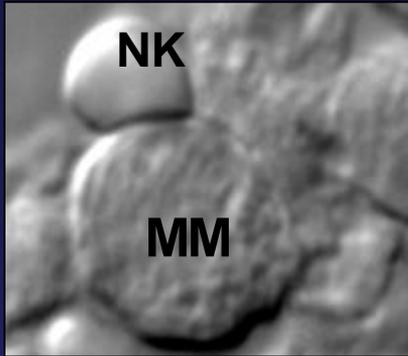
p-30



p-44



## NATURAL CYTOTOXICITY RECEPTORS



## SPONTANEOUS CYTOTOXICITY

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p-44



## NATURAL CYTOTOXICITY RECEPTORS

MICA/B/UL16-BP  
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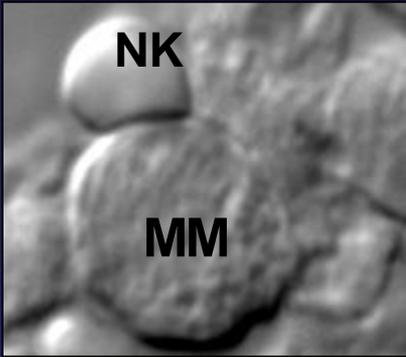
p-30



p-44



NATURAL CYTOTOXICITY RECEPTORS



MICA/B/UL16-BP  
Expressed on tumors  
of epithelial origin



## **NK cell control in allogeneic HCT: balance between inhibition and activation**

Anti-leukemic effects in HCT: maximize activation and minimize inhibition

NK alloreactivity due to “missing self”: obligate HLA-mismatched HCT

What KIR/HLA interactions can achieve the greatest anti-leukemic response in HLA-matched/compatible HCT?

# Donor KIR diversity makes donor selection based on KIR/HLA feasible

Genotype	3DL3	2DS2	2DL2	2DL3	2DP1	2DL1	3DP1	3DP1v	2DL4	3DL1	3DS1	2DL5	2DS3	2DS5	2DS1	2DS4	1D	3DL2	No.	(%) n=85
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P																			1	1.2
Q																			1	1.2
R																			1	1.2
S																			1	1.2
T																			1	1.2
U																			1	1.2
V																			1	1.2
W																			1	1.2
X																			1	1.2
Y																			1	1.2
Z																			1	1.2
AA																			1	1.2
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AJ																			1	1.2
	3DL3	2DS2	2DL2	2DL3	2DP1	2DL1	3DP1	3DP1v	2DL4	3DL1	3DS1	2DL5	2DS3	2DS5	2DS1	2DS4	1D	3DL2		

# Patients and Methods

## **STUDY POPULATION**

- 1277 pts with Acute Myelogenous Leukemia (AML)
- 664 HLA-matched 10/10
- 613 HLA-matched 9/10

**KIR GENOTYPING:** gene content, KIR2DS1 (33%), KIR3DS1 (34%)

**HLA GENOTYPING:** KIR ligands C1, C2

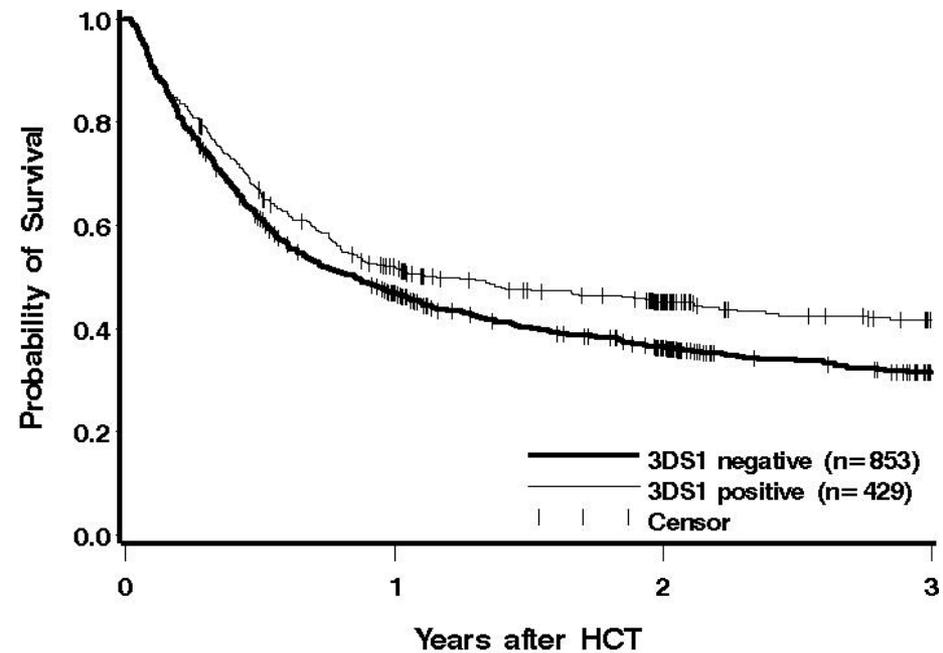
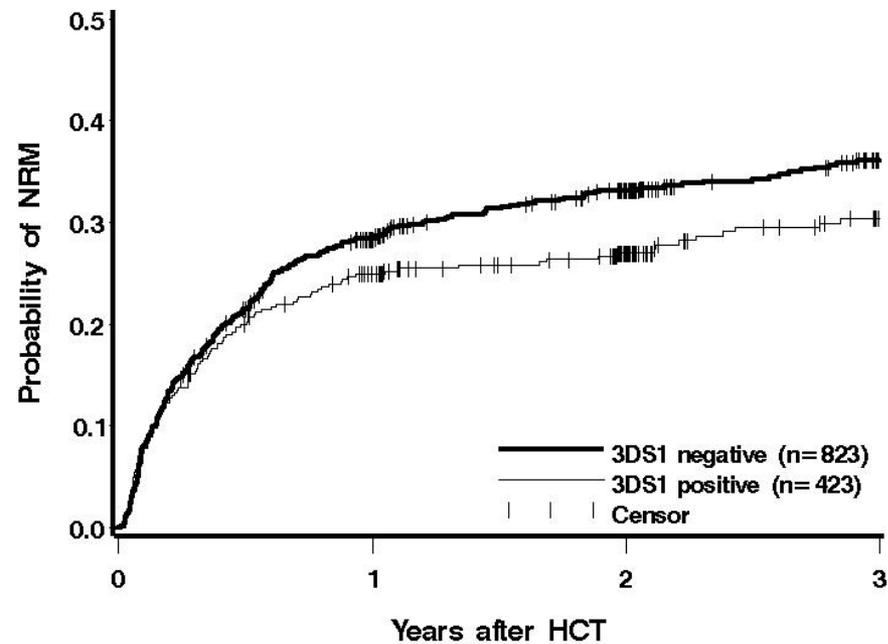
**OUTCOMES:** Survival, relapse, NRM, GvHD

**ANALYSIS:** (Primary) KIR2DS1 and HLA-C ligands  
(Secondary) KIR3DS1

Analyses adjusted for patient age, disease severity, HLA matching, type of disease, T cell depletion, CMV serostatus, conditioning regimen, cytogenetics.

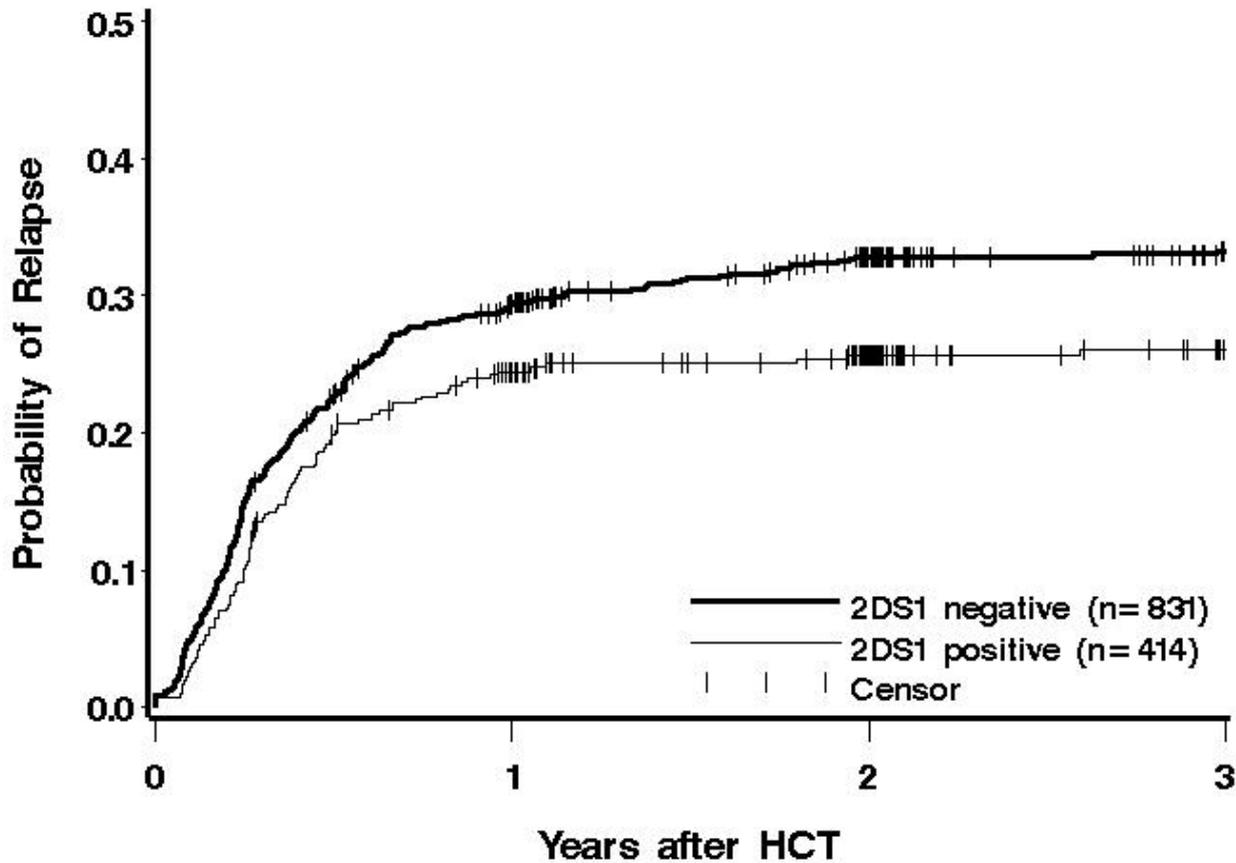
# Donor 3DS1: lower NRM and higher OS

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# Donor 2DS1 protects from AML relapse

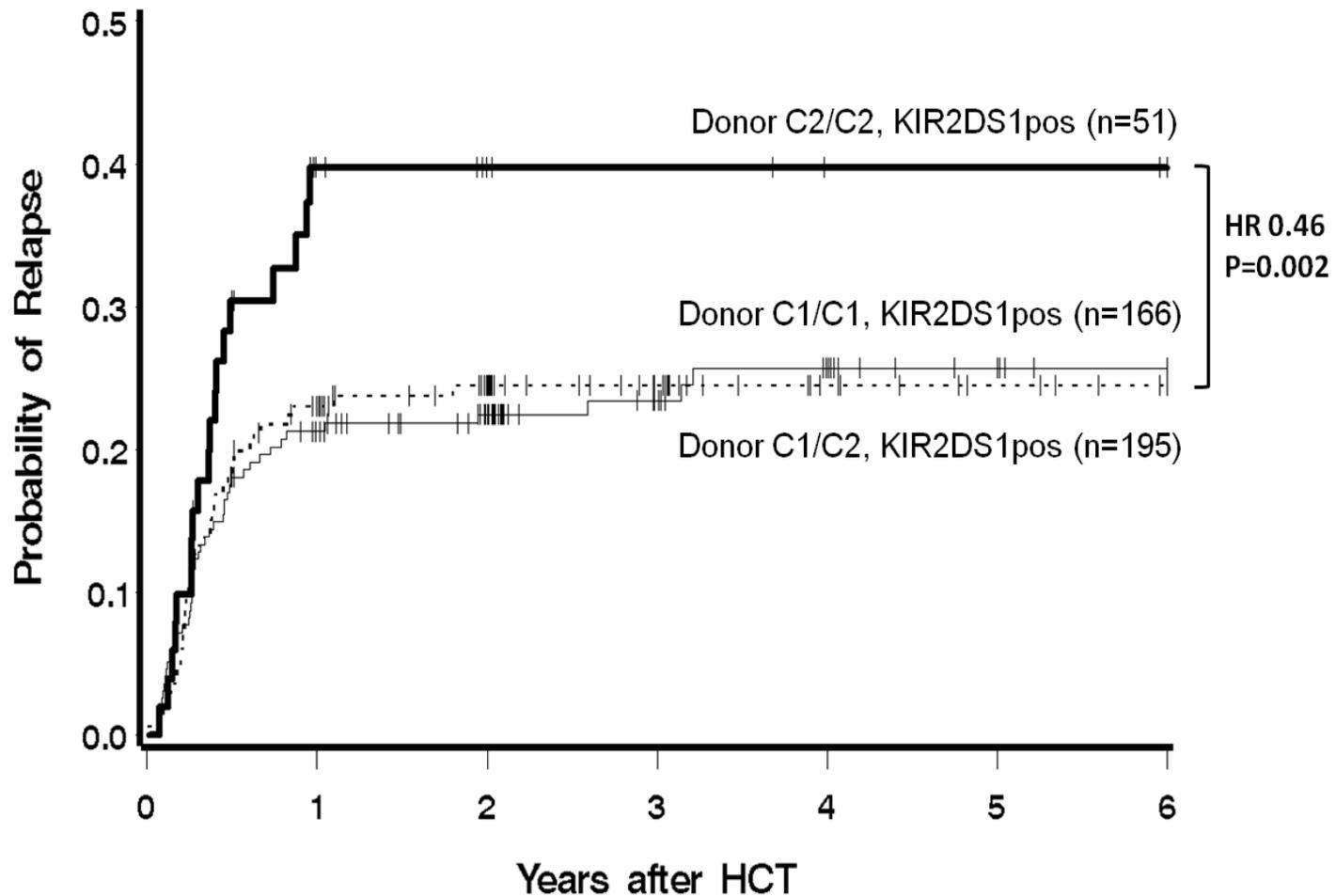
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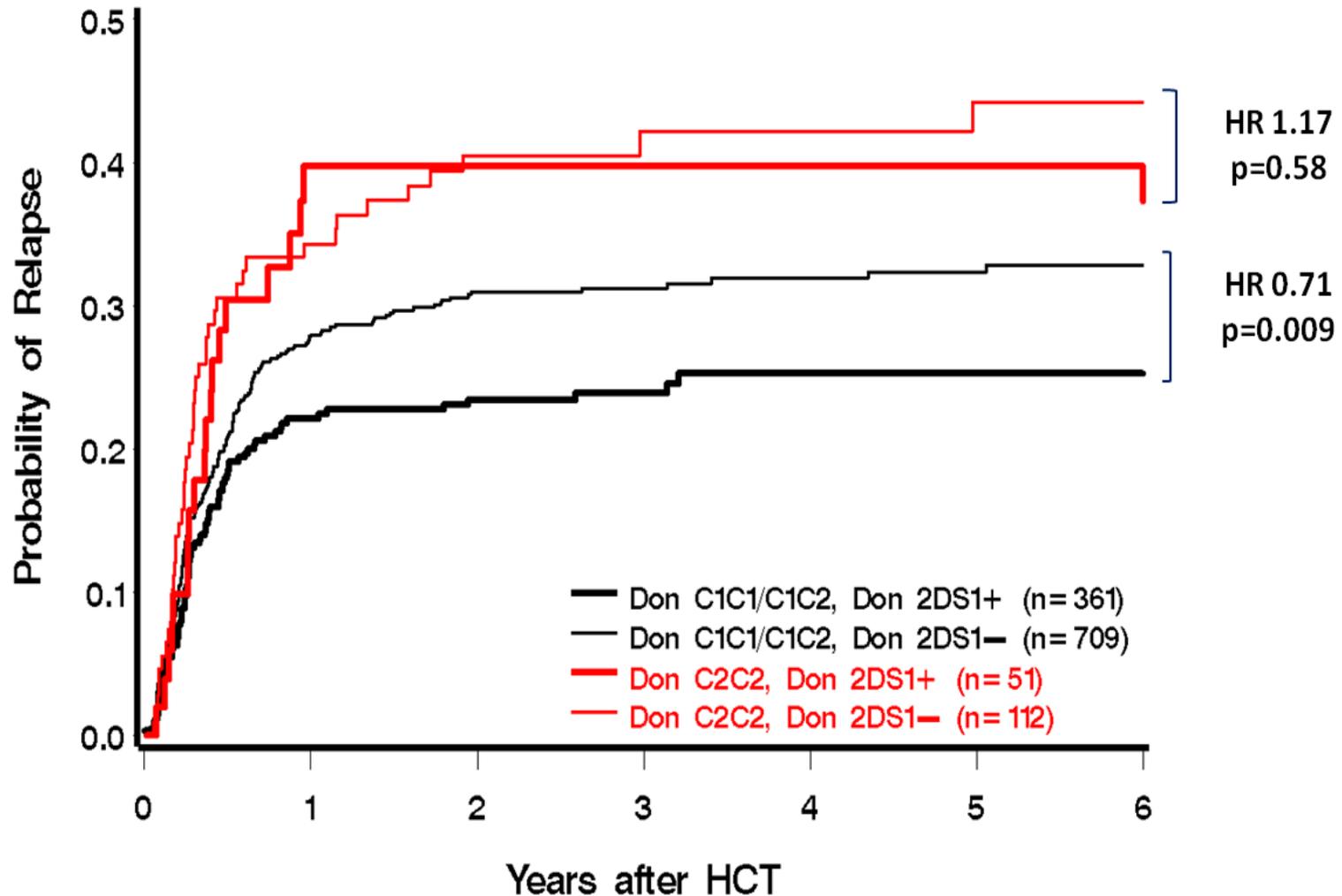
AML relapse: HR 0.76 (0.61-0.96),  $p=0.02$

# Donor 2DS1 effects are HLA-C restricted

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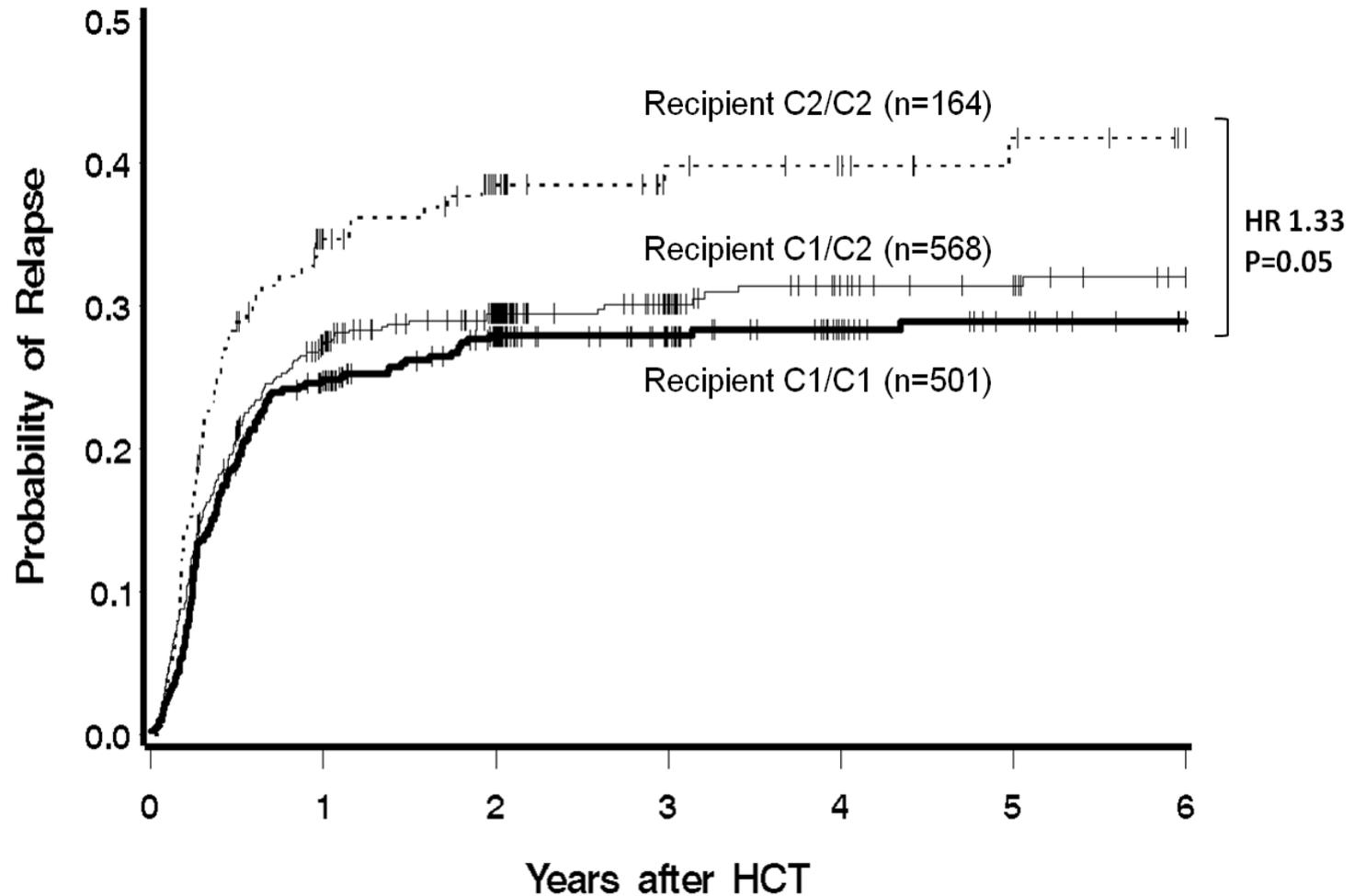


# Donor 2DS1 effects are HLA-C restricted



# Recipient HLA-C2C2 associated with higher relapse

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# Conclusions: activating KIR in HCT

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- There is a role for KIR genotyping in allogeneic HCT
- Greatest donor KIR effects in HSCT are seen in AML
- Activating KIR3DS1 impacts TRM and OS
- Activating KIR2DS1 impacts AML relapse in manner consistent with in vitro findings of NK education (C1) and tolerance (C2C2)

# Acknowledgments

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- Anthony Daniyan
- Ewelina Morawa

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- Gianfranco Pittari

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- Junting Zheng
- Shakeel Modak

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- Mari Malkki (FHCRC)
- Ted Gooley (FHCRC)
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- Mike Haagenson (NMDP)
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