Natural Killer cell therapy in myeloid disease

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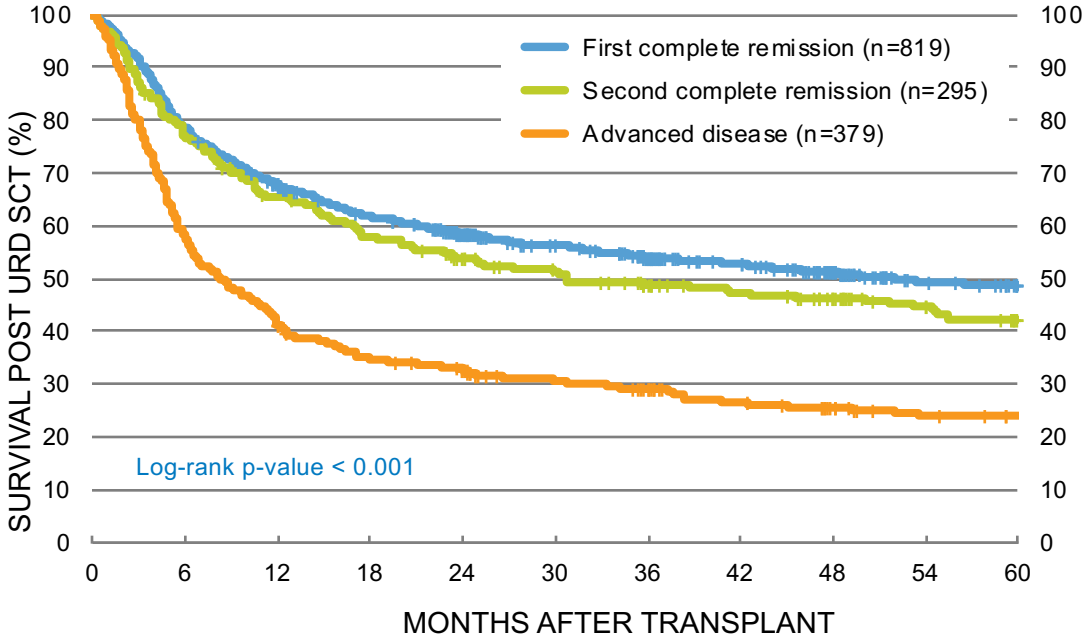
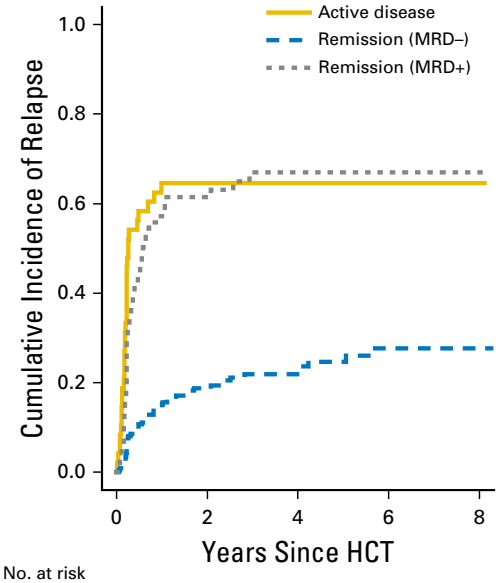
There is an unmet need to improve outcome in Acute Myeloid Leukemia

The majority of AML patients relapse whatever treatment they receive



SOURCE: CIBMTR®, the research program of NMDP/Be The Match

Relapse risk is highest for MRD+ patients



No. at risk					
Active disease	48	6	6	4	2
Remission (MRD–)	235	127	73	29	7
Remission (MRD+)	76	11	6	3	2

Araki et al. J Clin Oncol 34:329-336.2015

Adoptive cell therapy holds promise for MRD eradication in the the pre and post HSCT setting

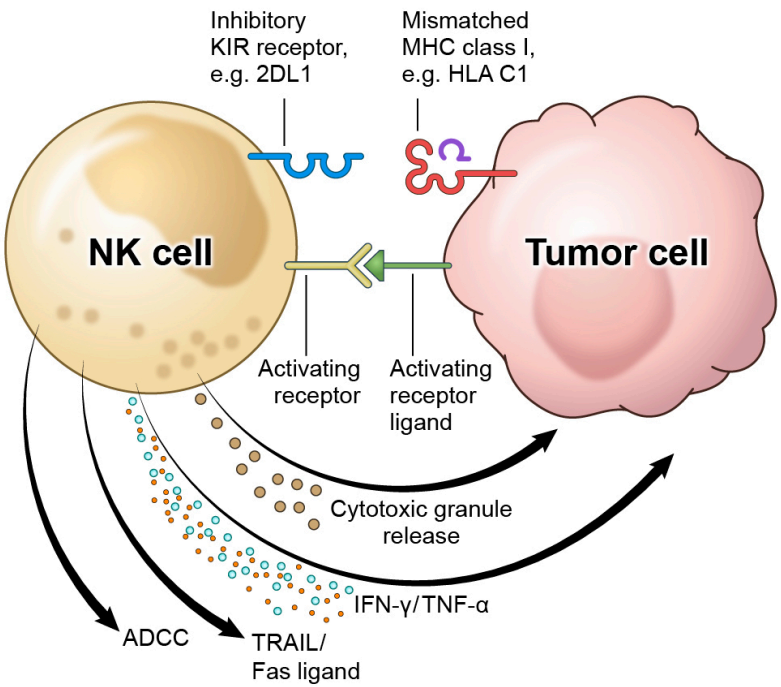
Potential problems with CAR T cells in AML

1. AML antigens eg. CD33 also expressed on normal hematopoetic SC: Cytopenia

2. Cytokine Release Syndrome

3. GVHD when given post HSCT

NK cells may offer a useful alternative to T cell therapy to reduce relapse risk in myeloid disease



Directly kill myeloid blasts

Don't have antigen-dependent recognition

Do not require HLA match

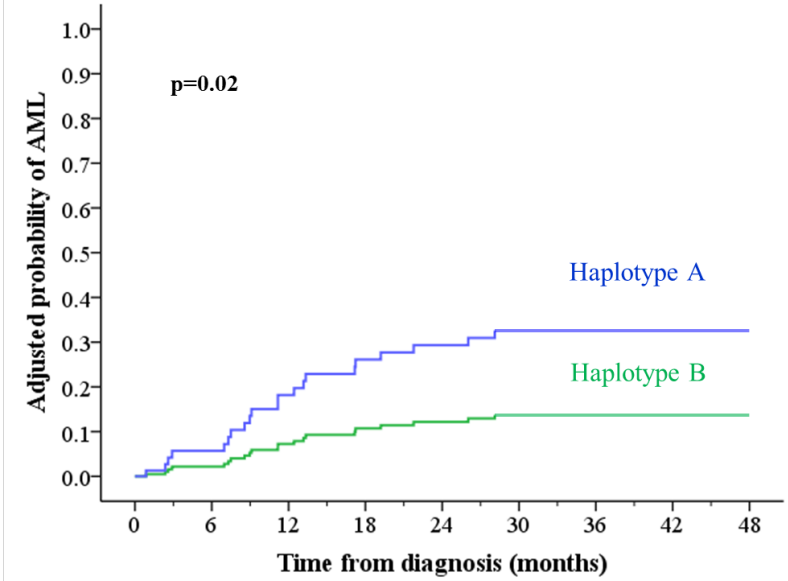
- -GVHD not a problem
- -Potential for off the shelf product with consequent cost benefits

If we can give increased numbers of effective NK cells this may facilitate clearance of MRD and reduce relapse

Evidence supporting the importance of the NK cell immunity in AML/MDS

MDS patients with a more 'activating' NK cell receptor repertoire (KIR B haplotype) were less likely to progress to AML

A MDS: Adjusted probabilities for progression to AML according to KIR haplotype



Patients at risk

Haplotype A	28	15	11	8	5
Haplotype B	80	53	37	26	20

N=108 MDS patients
N=499 AML patients v 253 HC

Independent predictor in the multivariate models (IPSS, cytogenetic risk group, age, WHO type)

KIR Gene Haplotype: an Independent Predictor of Clinical Outcome in MDS Patients, Stringaris et al. *Blood* 2016 ; 128, 24.

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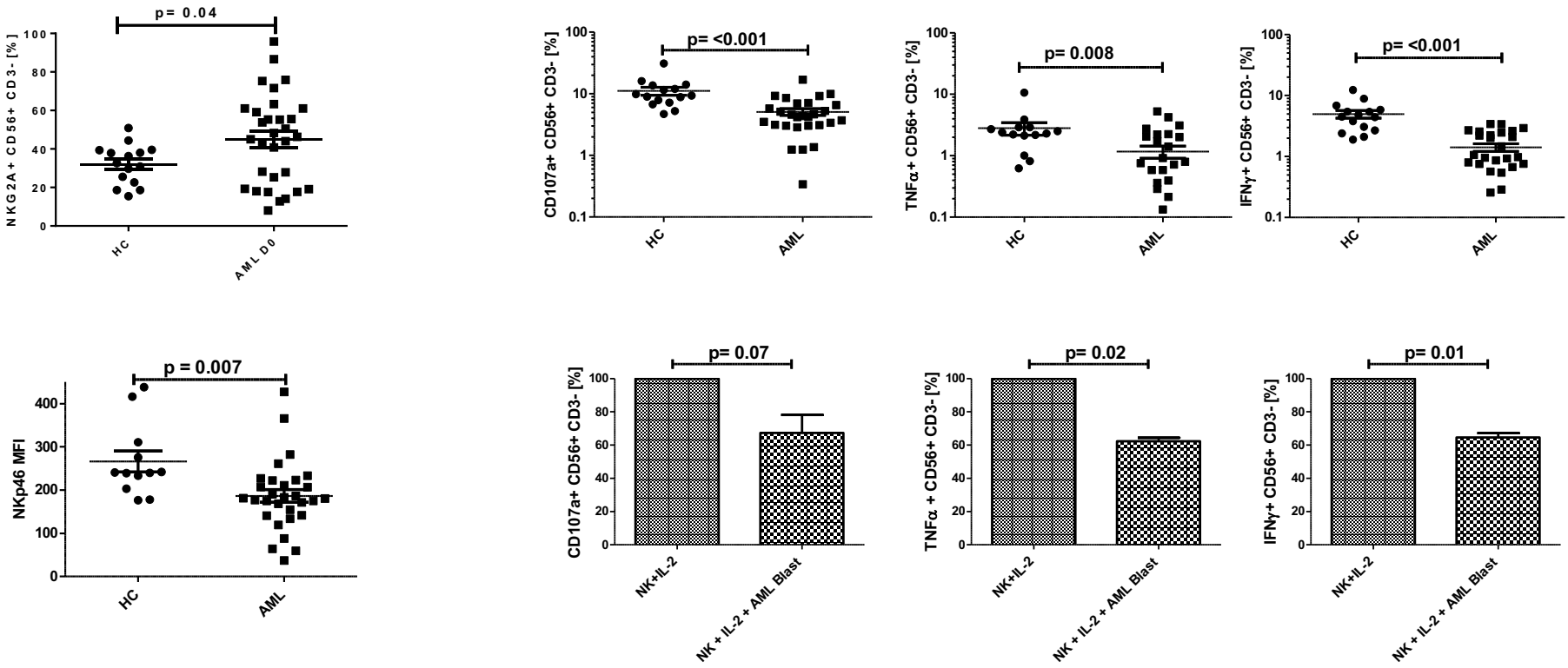
Evidence supporting the importance of the NK cell immunity in AML/MDS

NK surface phenotype and effector function is abnormal in AML compared to healthy controls and these abnormalities could be induced in healthy donor NK cells after incubation with AML blasts



Stringaris et al. Haematologica, 2014 May;99(5):836-47

NK cell immunotherapy trials for hematological malignancy

Cell source	Indications	Conditions for expansion/activation of cell product	Ref
Allo NK	AML/MDS	IL15/IL21	NCT00569283
Allo NK	AML	IL-2	NCT00799799
Allo NK	AML	IL15	NCT02395822
Auto NK	MM	K56241BB expn	NCT02481934
Auto NK	Solid tumor, CLL, myeloma	Expanded in IL2 for 14d	NCT
NK-92 cell line	Leukemia and lymphoma	CD7 CAR CD28, 4-1BB, CD3ζ	NCT02742727
NK-92 cell line	CD33 + acute myeloid leukemia	CD33 CAR CD28, 4-1BB, CD3ζ	NCT02944162

Adoptive NK cell therapy protocol 08-H-0816
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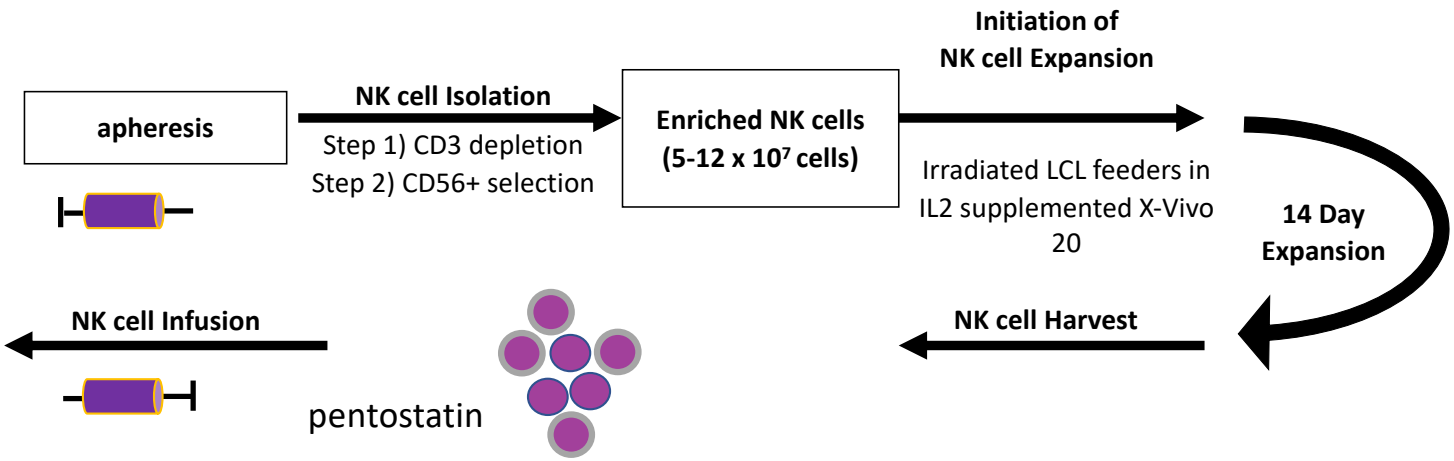
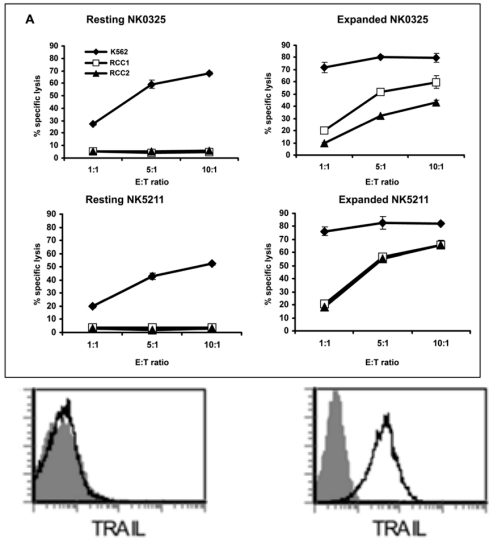


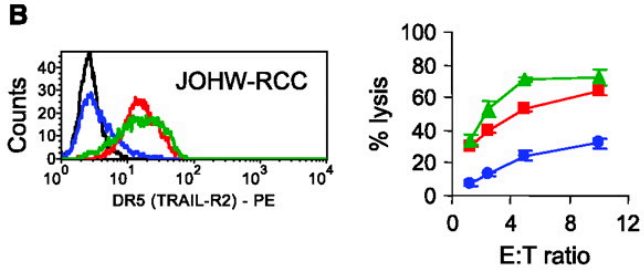
Doses up to 5 x 10^8/kg

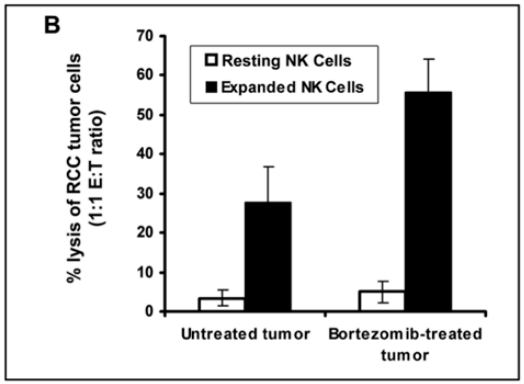
Resting NK **Expanded NK**



Bortezomib upregulates TRAIL receptor DR5 on tumor cells

-green line represents Bort treated cells, blue untreated





Lundqvist et al. Ca Res 2006, Berg et al. Cytotherapy. 2009 ; 11(3): 341–355

Tracking NK cell homing with ^{89}Zr and PET/CT

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Isolating, expanding and labeling NK cells with ^{89}Zr prior to infusion into animal and PET/CT imaging

50ml blood draw

NK cell Isolation

Step 1) CD3 depletion
Step 2) NKp80+ selection

Enriched NK cells (5-12 x 10^7 cells)

Initiation of NK cell Expansion

Irradiated LCL feeders in IL2 supplemented X-Vivo 20

14 Day Expansion

NK cell Harvest

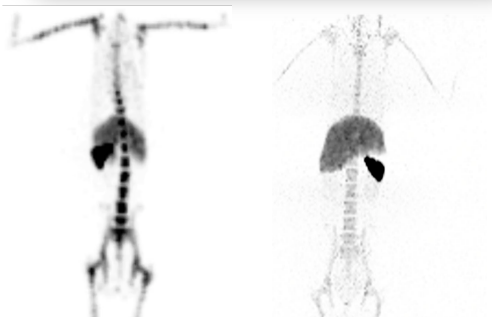
89Zr-oxine labeling of NK cells

^{89}Zr

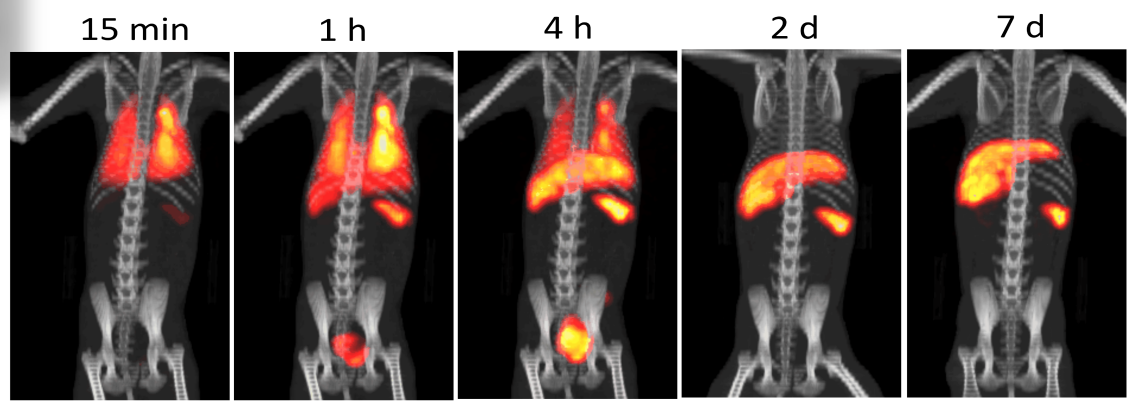
NK cell Infusion

Serial PET/CT scan

^{89}Zirconium labelled expanded autologous NK cells visualized by PET/CT for up to 7 days post infusion in RM



CD34+ Expanded NK



Can be used as a method to assess validity of new strategies to improve NK homing to bone marrow

We plan to use this model in human clinical trials in near future

How to improve therapeutic efficacy of NK immunotherapy

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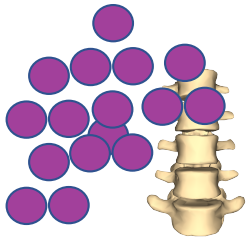
Strategies to improve bone marrow homing

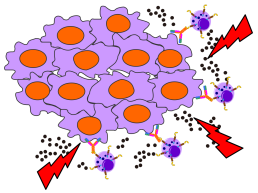


a. Fucosylation

b. Optimisation of homing via CXCL10/CXCR3 with IFN alpha

c. Transduction of homing receptors eg CXCR4

Strategies to improve cytotoxicity towards myeloid cells



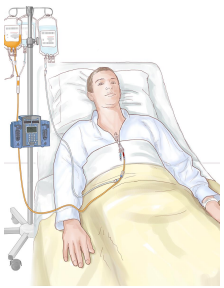
a. Bortezomib

-TRAIL receptor upregulation

-HLA E /c-flip downregulation

b. Enhanced ADCC

Potential opportunities for Autologous and Allogeneic NK cellular therapy



AML/High risk MDS

Induction chemotherapy

Remission

Apheresis

consolidation chemotherapy

consolidative autologous NK cell immunotherapy

Generation of NK cell Product

- Expand and activate NK cells ex vivo
- Genetic modification of NK cells
  - Improve homing, killing

Long term remission

Remission

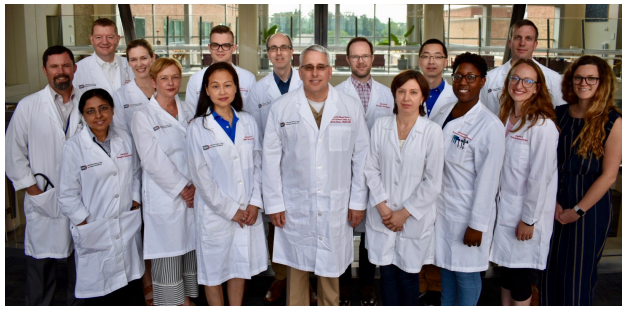
Donor Apheresis + Allograft Collection

allogeneic stem cell transplantation

consolidative allogeneic NK cell immunotherapy

Summary

- NK cell therapy has potential to improve outcome in myeloid malignancies
- More preclinical work to be done to create the optimal NK cell product and to optimize when/where to give it



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