1st CUNEO CITY IMMUNOTHERAPY CONFERENCE (CCITC) -May 17-19 2018-

IMMUNOTHERAPY IN HEMATOLOGICAL MALIGNANCIES 2018

Exploiting NK-cell alloreactivity in AML

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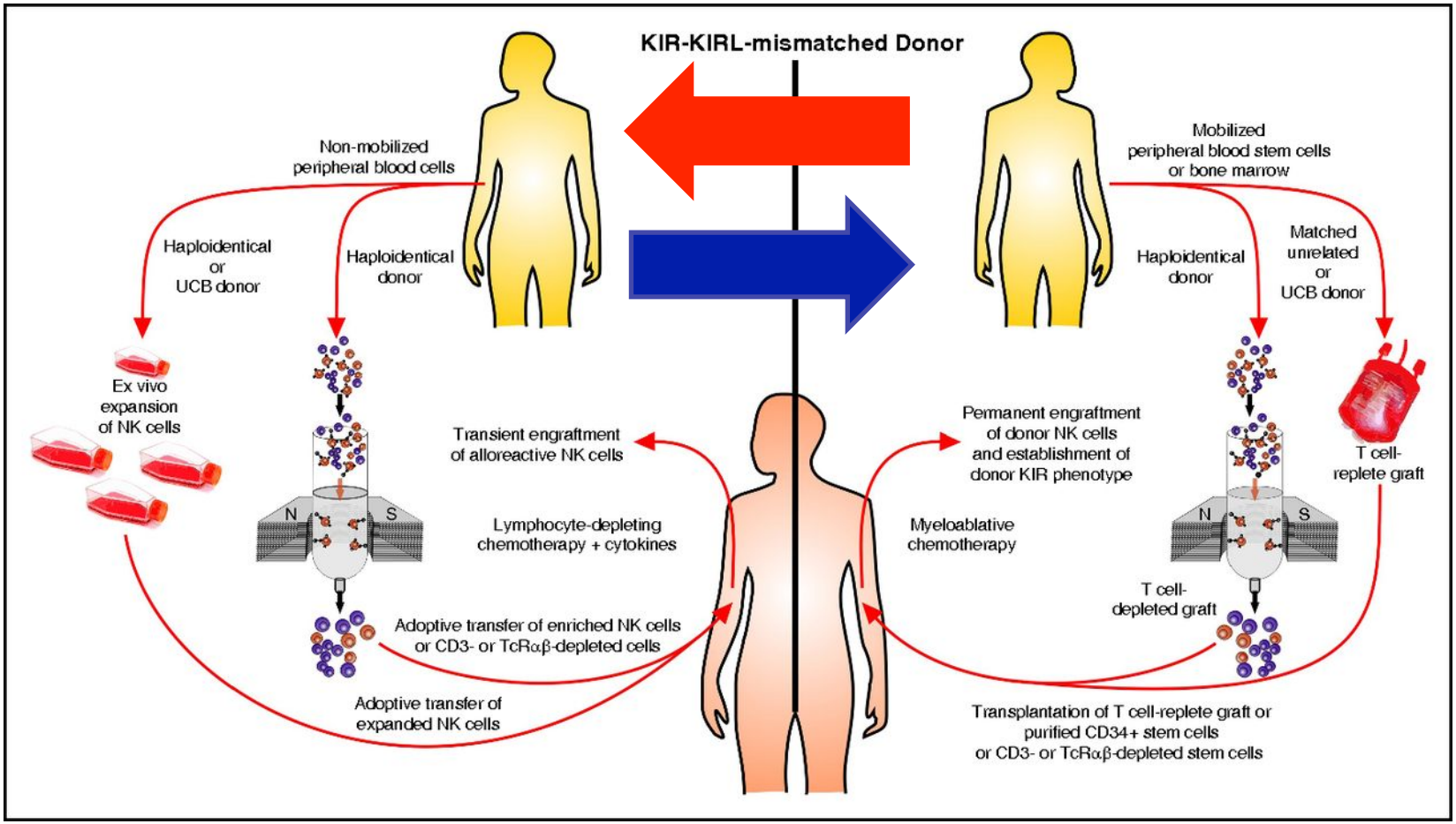
Clinical exploitation of alloreactive NK cells

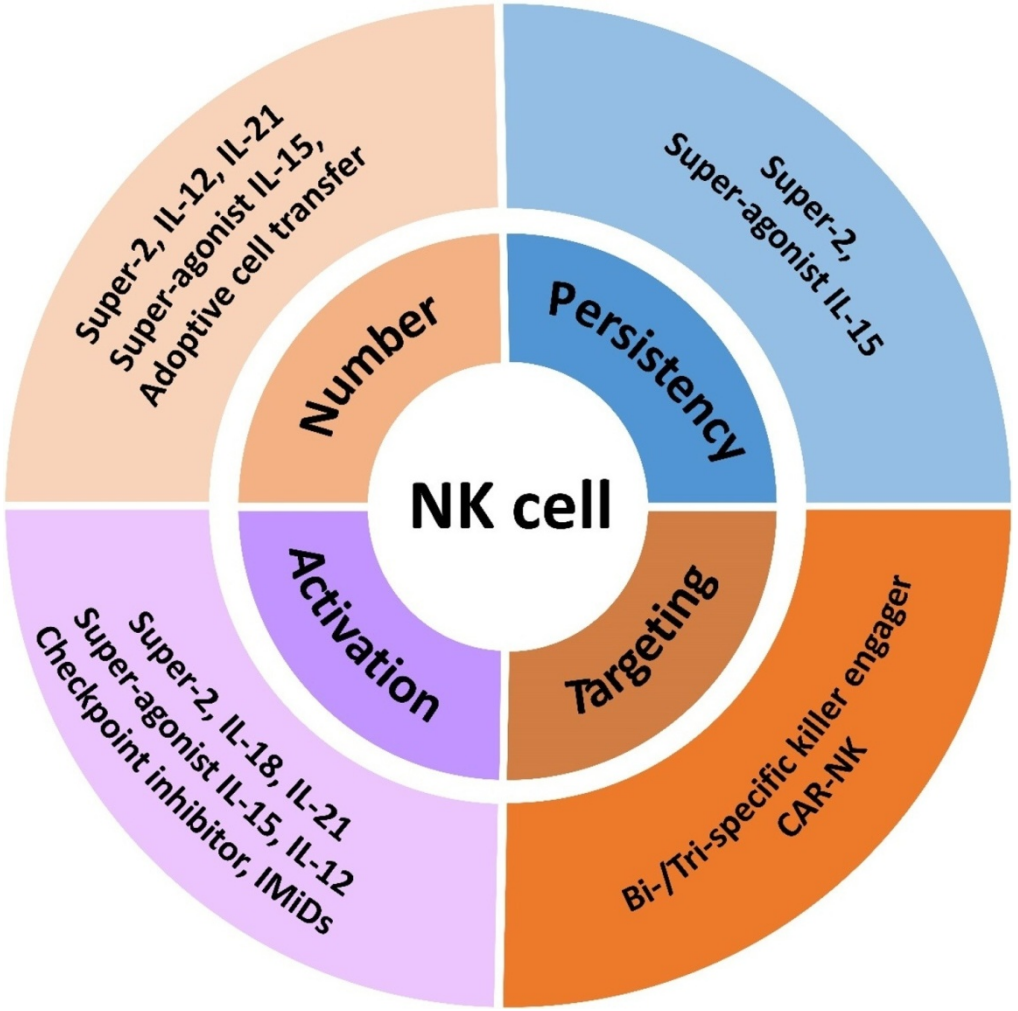
Adoptive immunotherapy

HSCT



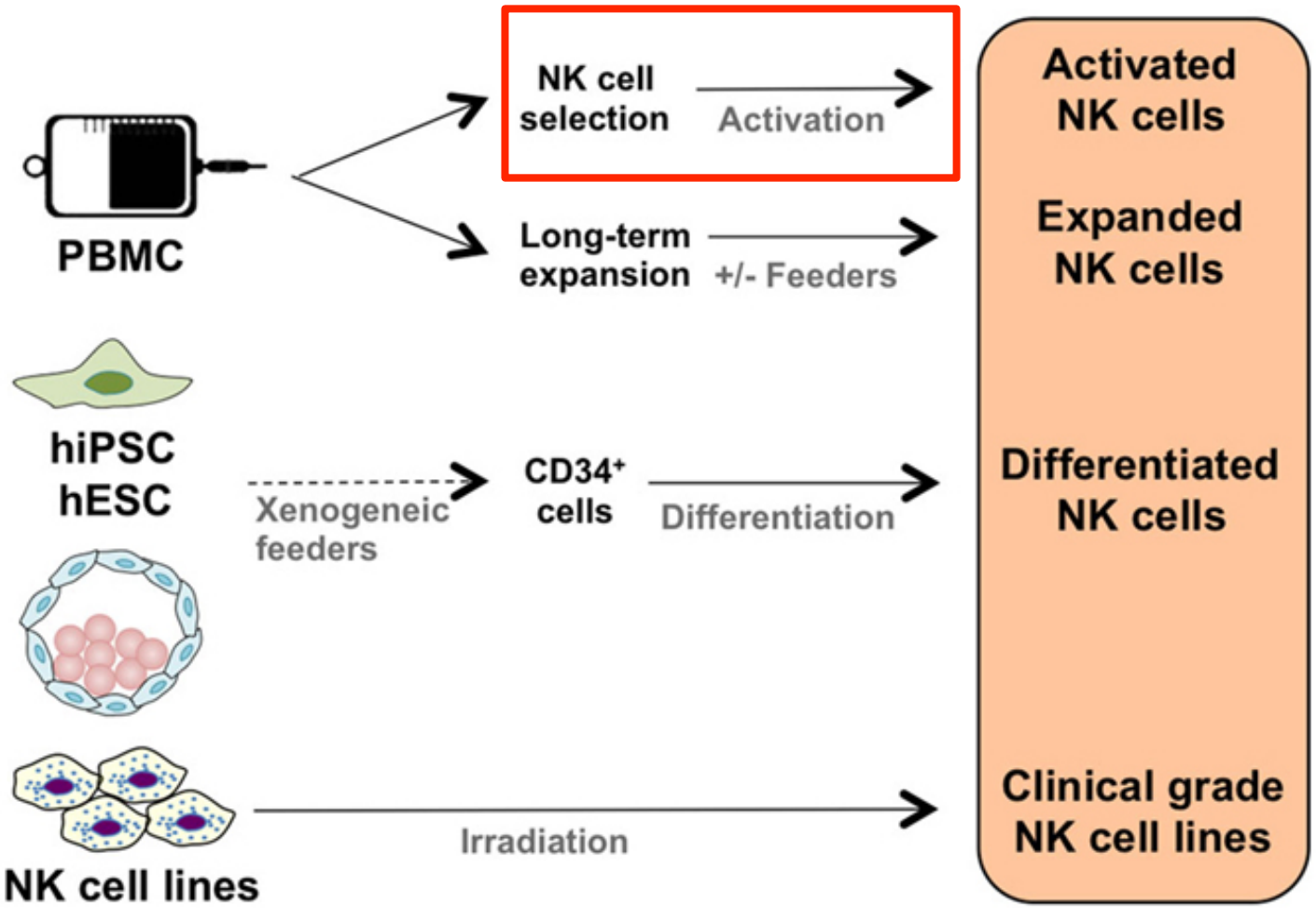
Handgretinger et al. Blood 2016

Factors influencing NK-cell based immunotherapy against cancer

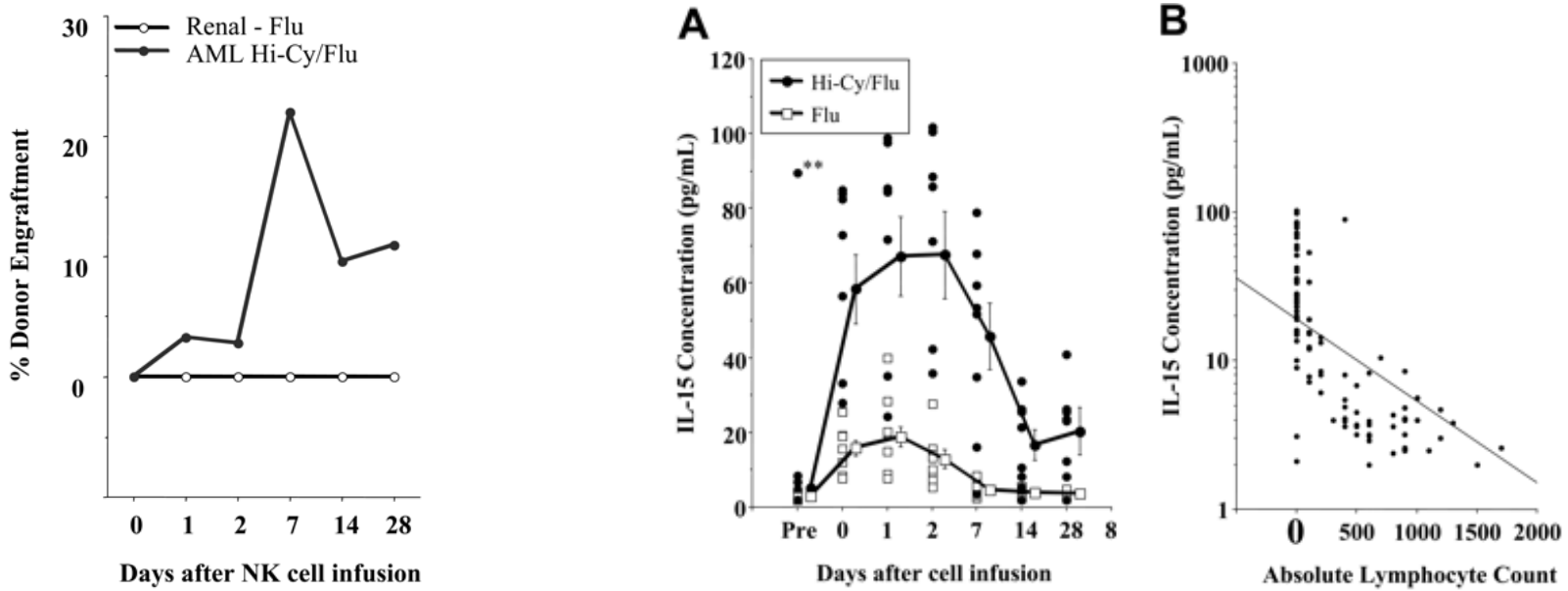


Fang et al. Semin Immunol, 2017

Different manufacturing strategies to obtain NK cells are under investigation



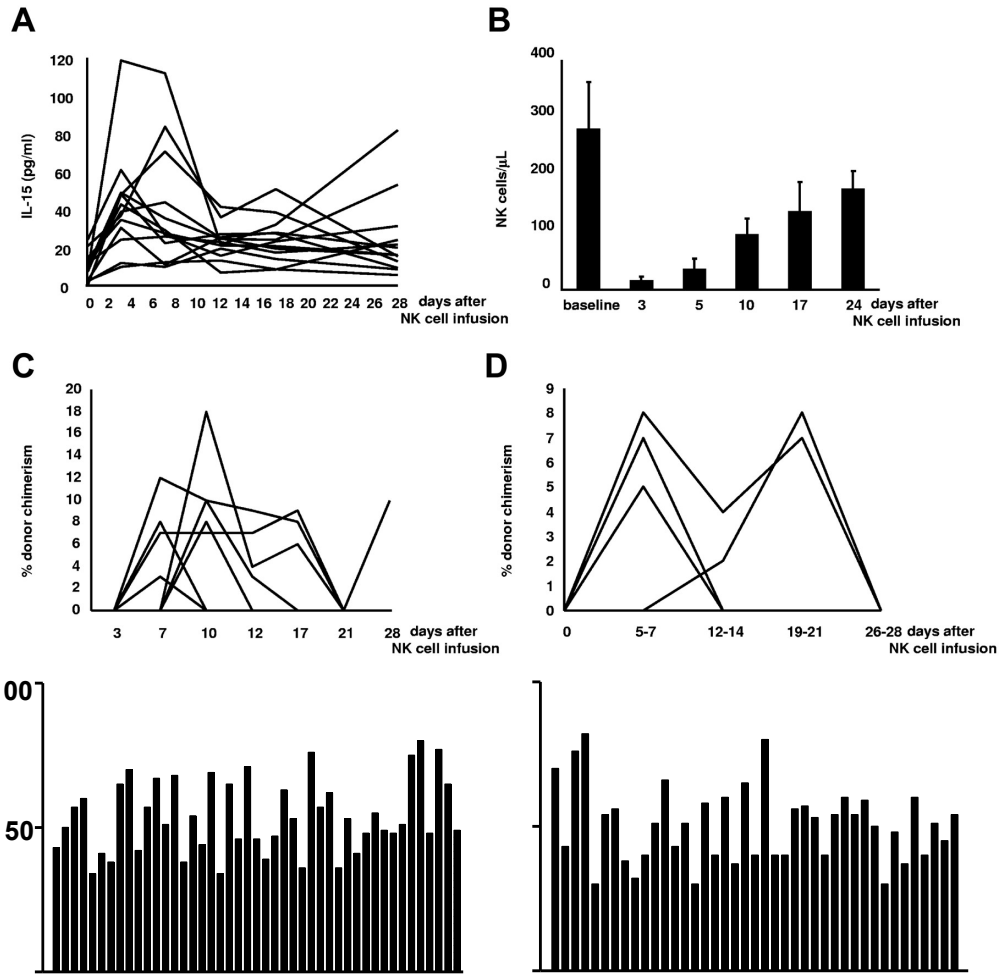
Expansion of haploidentical NK cells after infusion into cancer patients



Five/19 poor-prognosis patients with AML achieved complete remission after infusion of partially purified haploidentical NK cells.

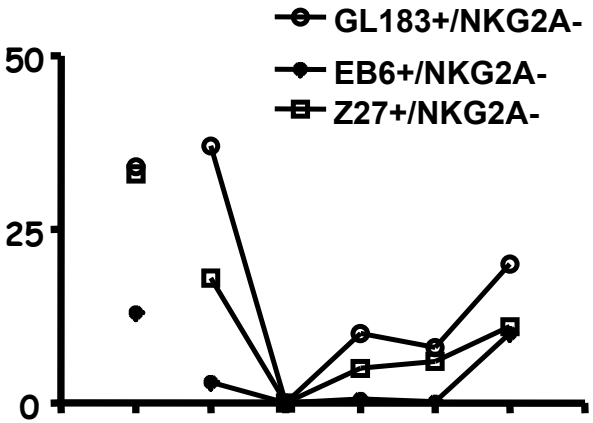
Miller et al. Blood 2005

Infused NK cells are alloreactive against AML

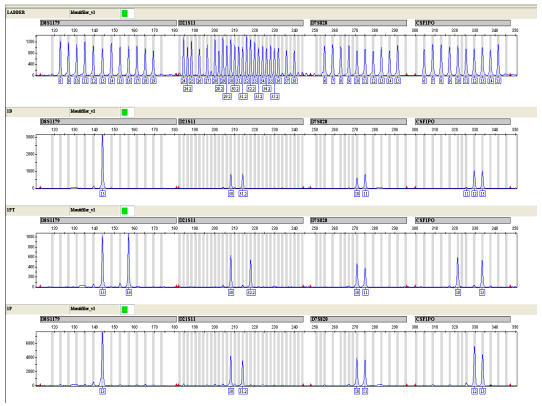


HLA-C1^{+} donor alloreactive
NK clones in C1 missing patients

HLA-C2^{+} donor alloreactive
NK clones in C2 missing patients



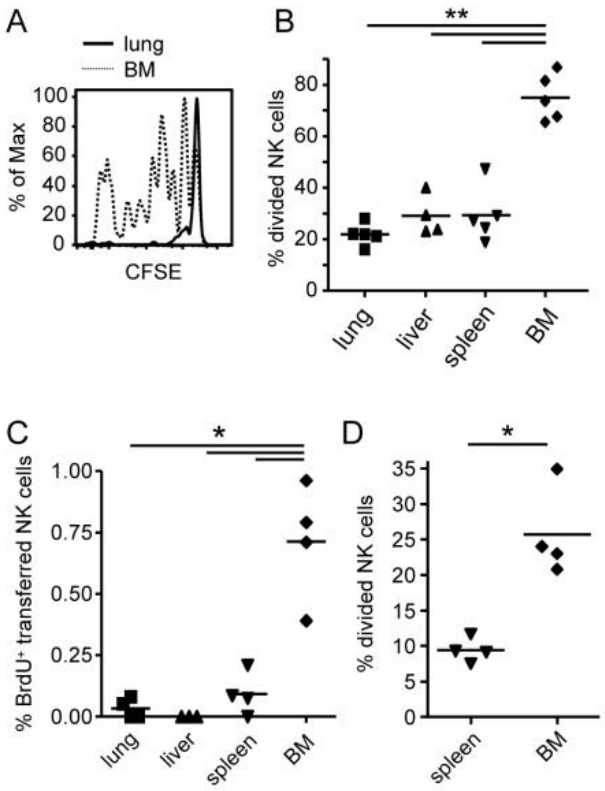
VNTR analysis



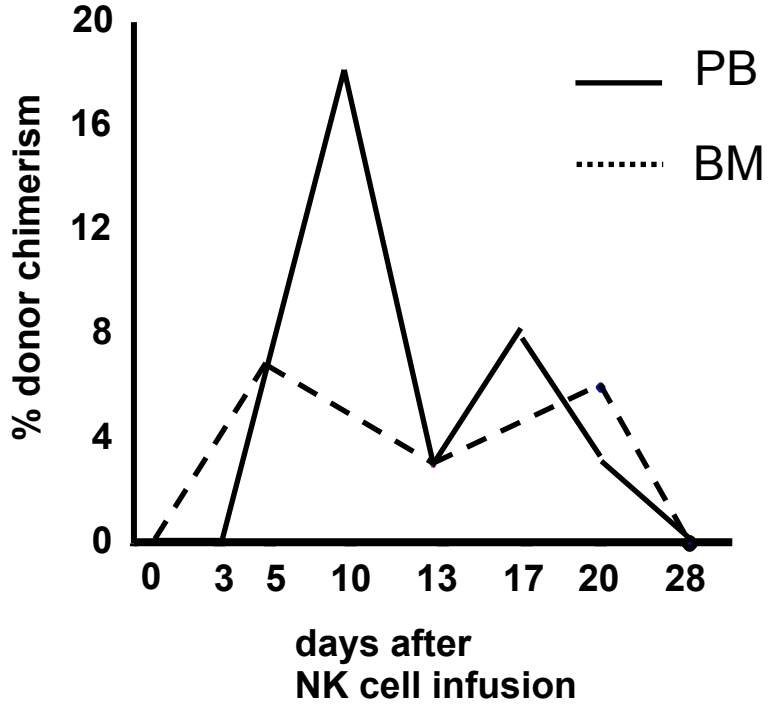
Curti et al. Blood 2011

Infused NK cells are capable of homing in recipient's bone marrow

Long-lived NK cells proliferate homeostatically in the BM

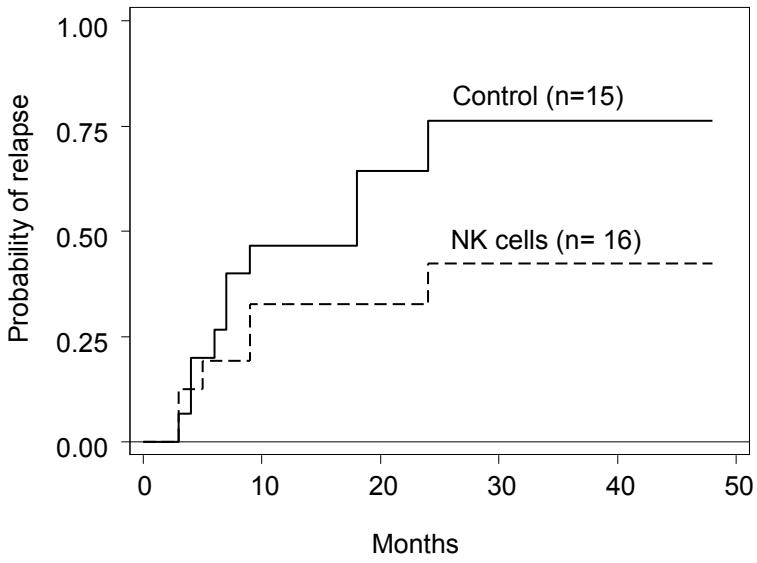


Van Helden MJ et al. J Immunol 2012

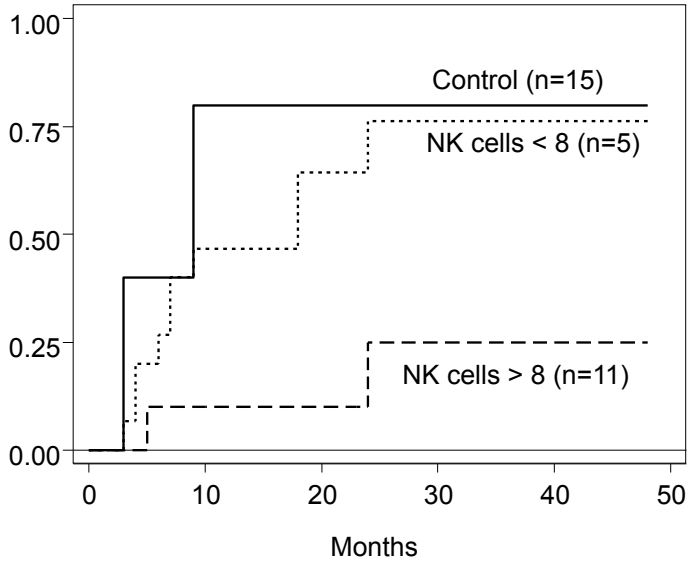


Curti et al. Blood 2011

Larger NK alloreactivity is associated with reduced relapse



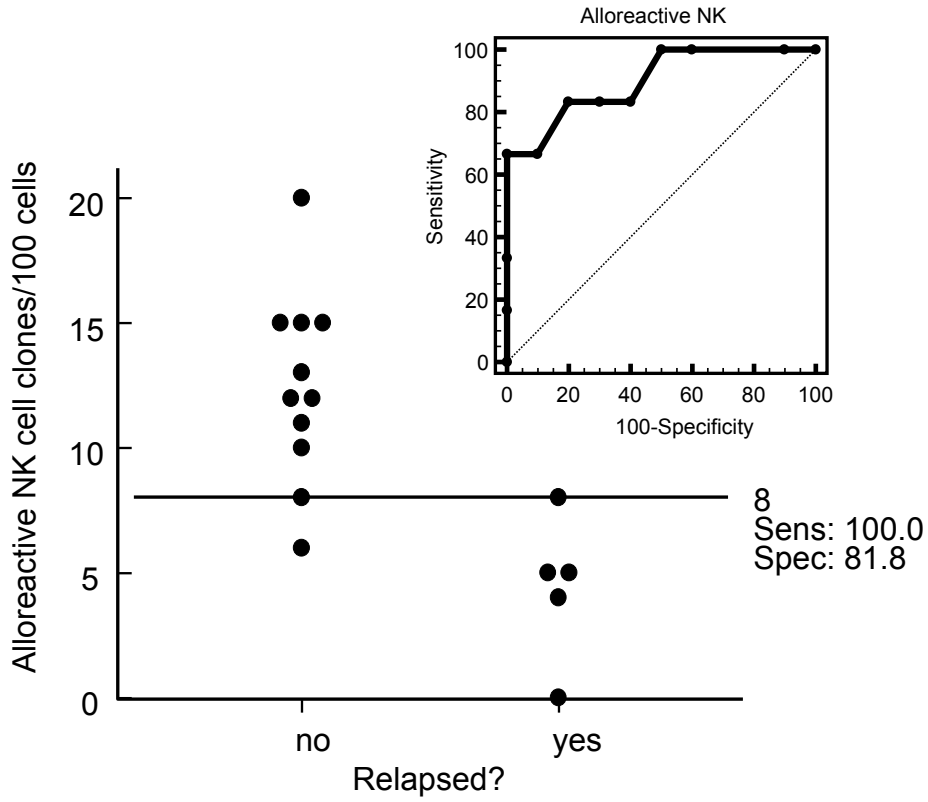
NK cells vs. control
HR 0.49 (95% 0.18-1.30)
P=0.138 Log Rank test

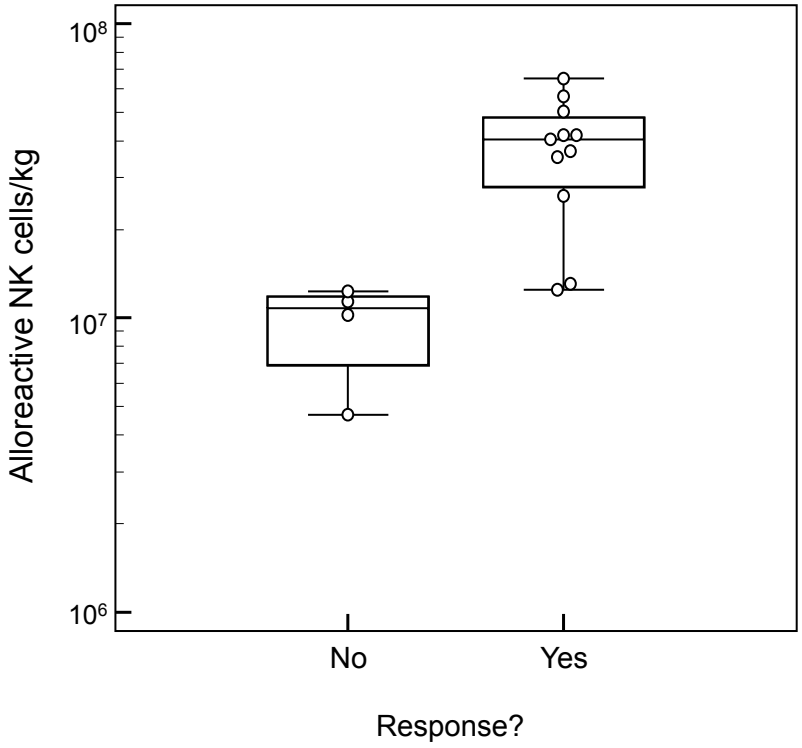


NK >8 vs. control
HR 0.15 (95% 0.03-0.70)
P=0.03 Log Rank test

Curti et al, Clin Cancer Res, 2016

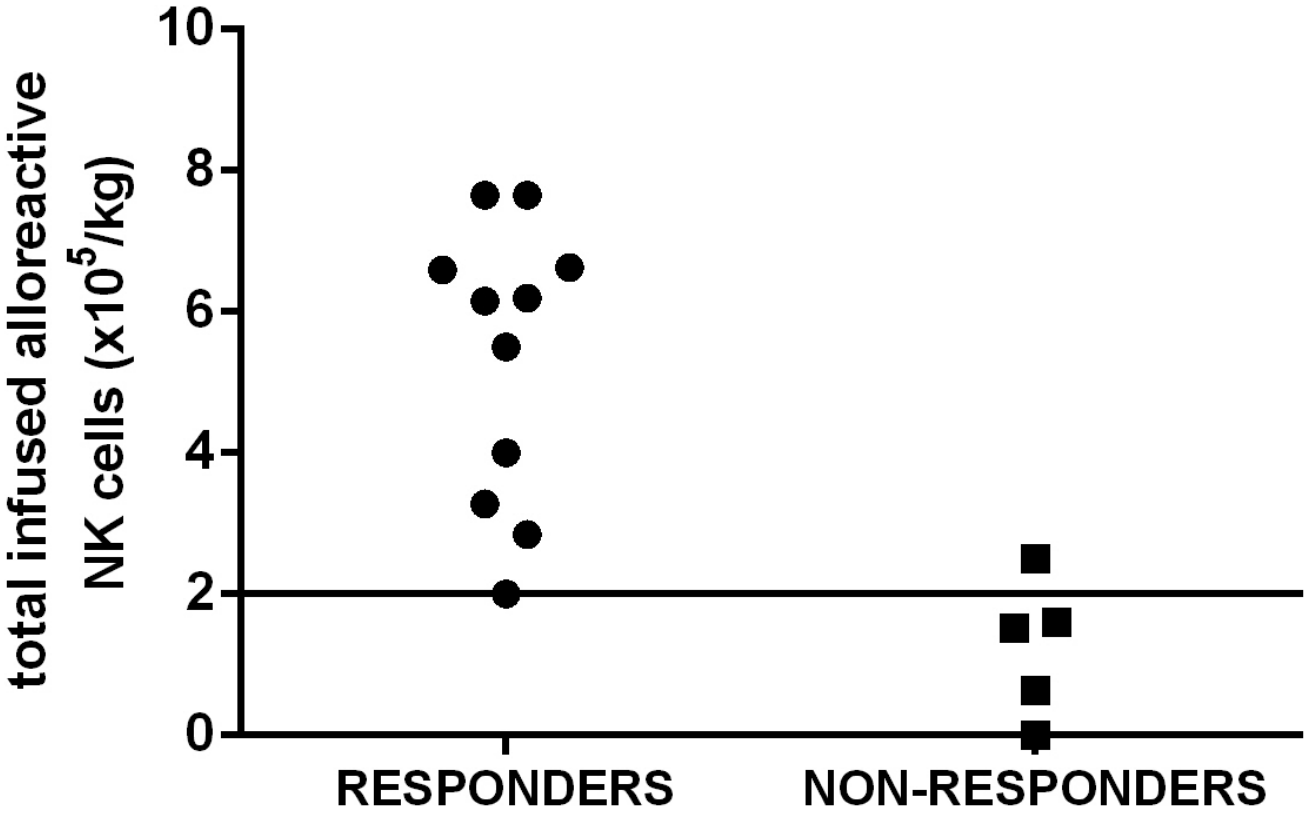
A threshold of alloreactive NK cell clones is predictive for response





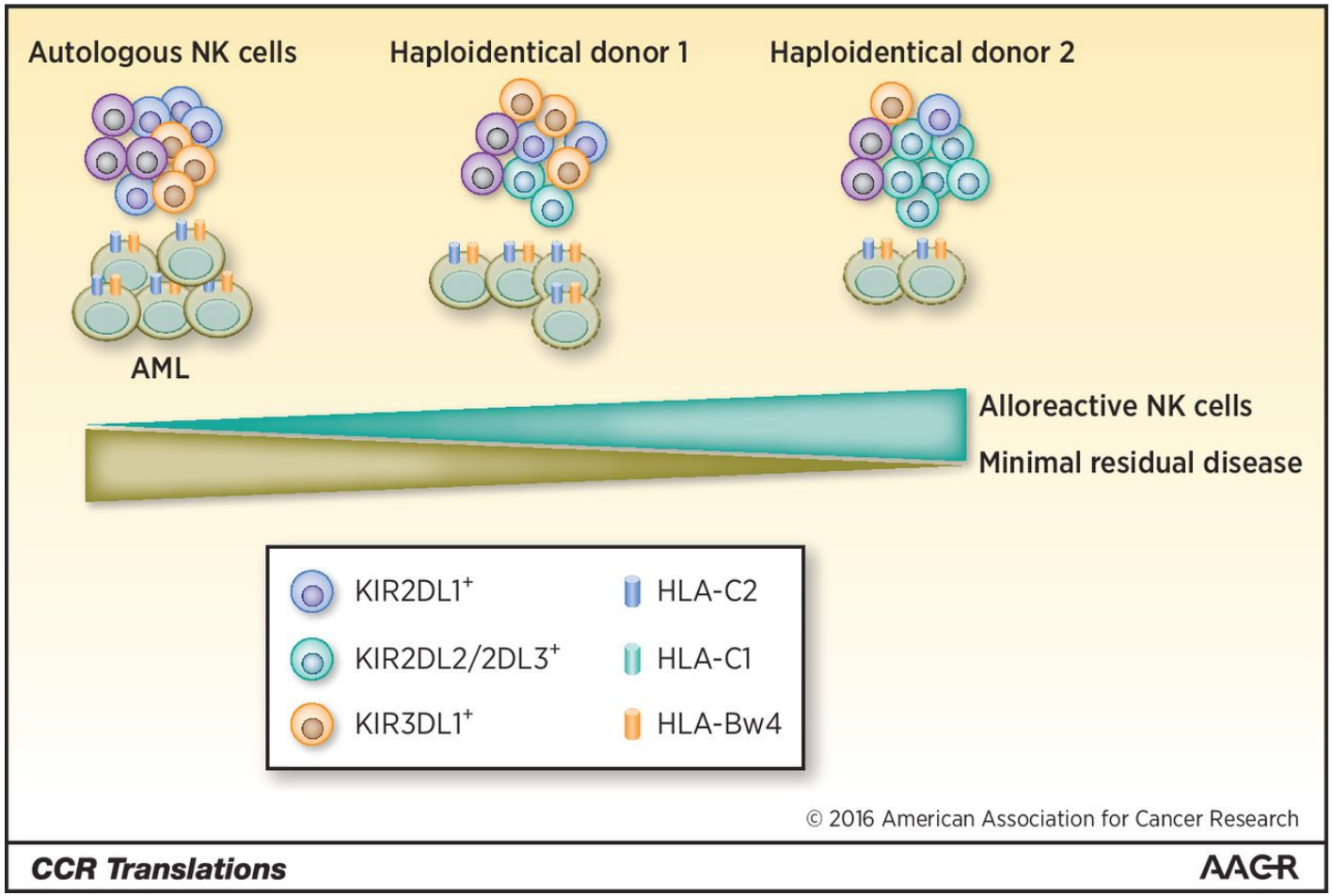
Curti et al, Clin Cancer Res, 2016

A threshold of alloreactive NK cell cells is predictive for response



Parisi et al, Front Immunol, 2017

The frequency of alloreactive NK cells may impact on the control of MRD in AML

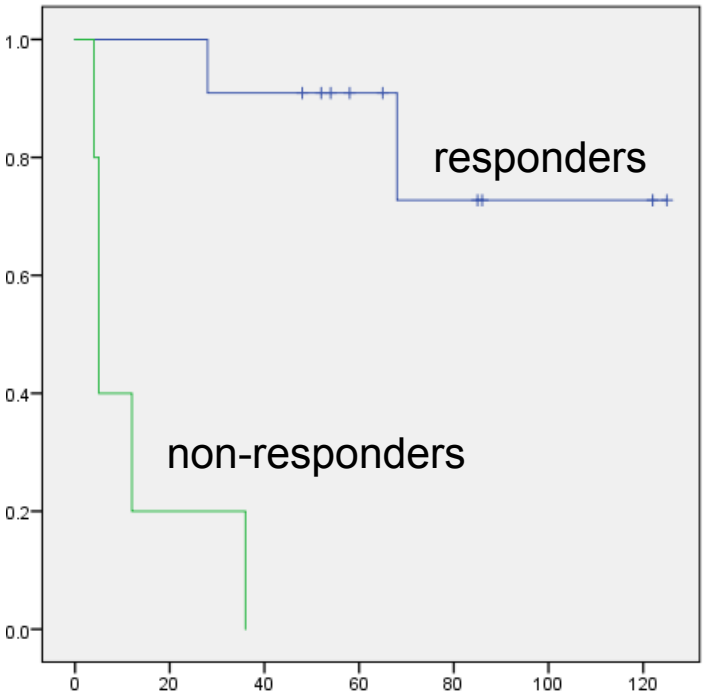


Aura Muntasell, and Miguel López-Botet Clin Cancer Res 2016;22:1831-1833

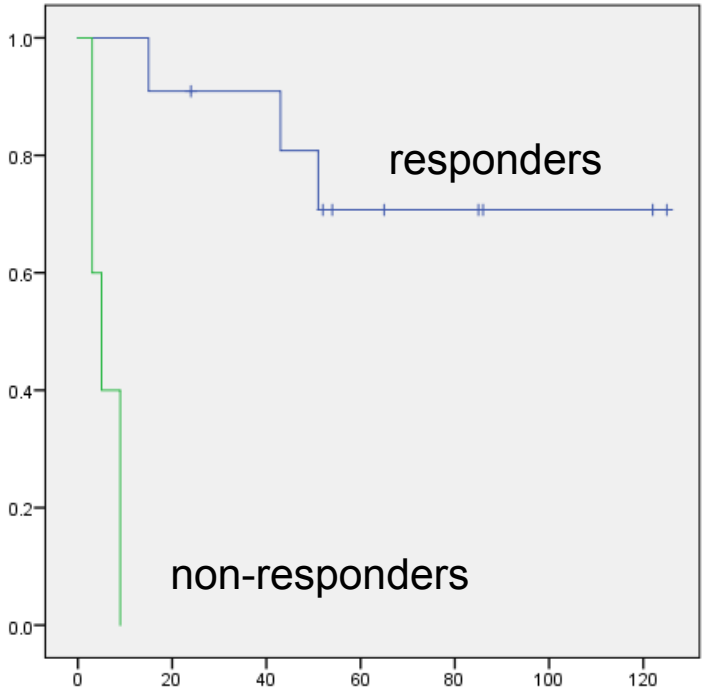
Clinical Cancer Research
AACR American Association for Cancer Research

Response to NK infusion predicts durable remission after long-term follow up

Overall Survival



Disease-free Survival

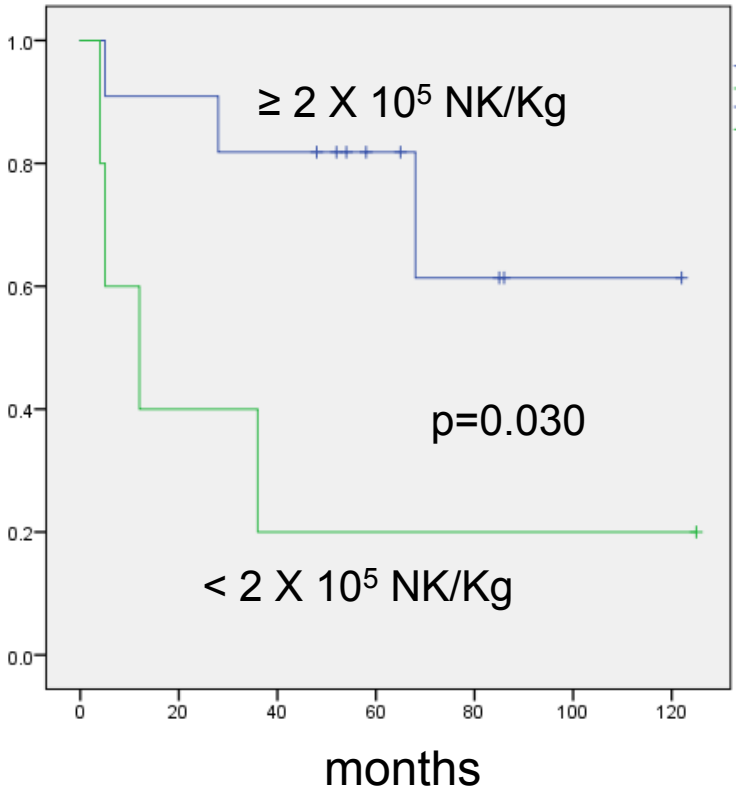


p=0.0001

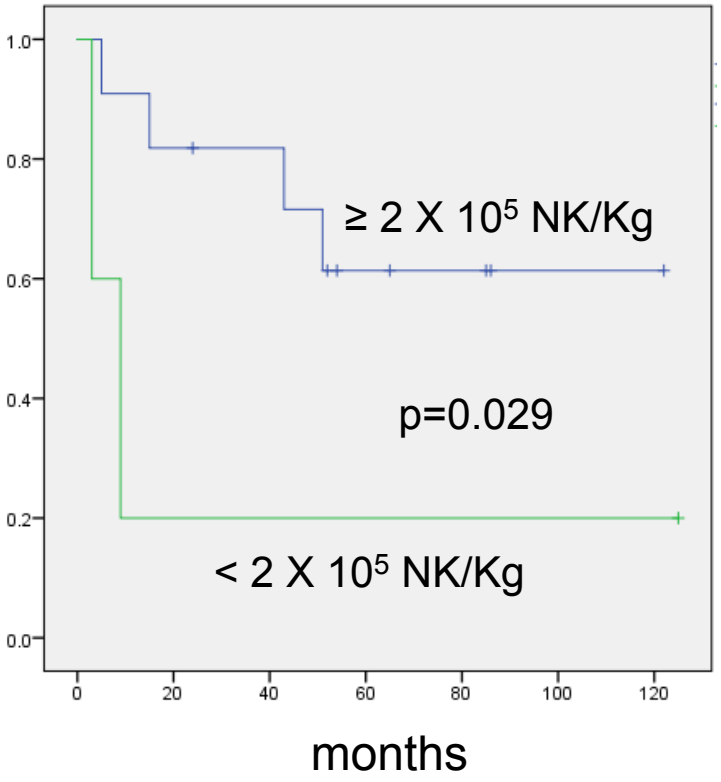
Parisi et al, EHA, 2018

The number of infused donor NK alloreactive cells correlates with prologed OS and DFS

Overall Survival

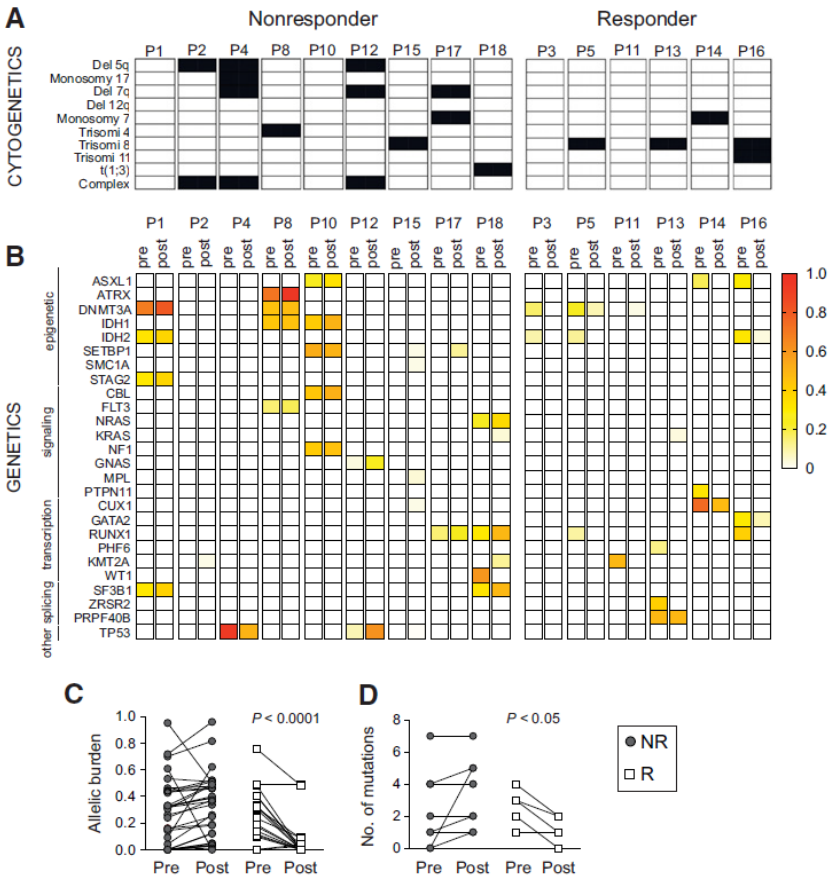


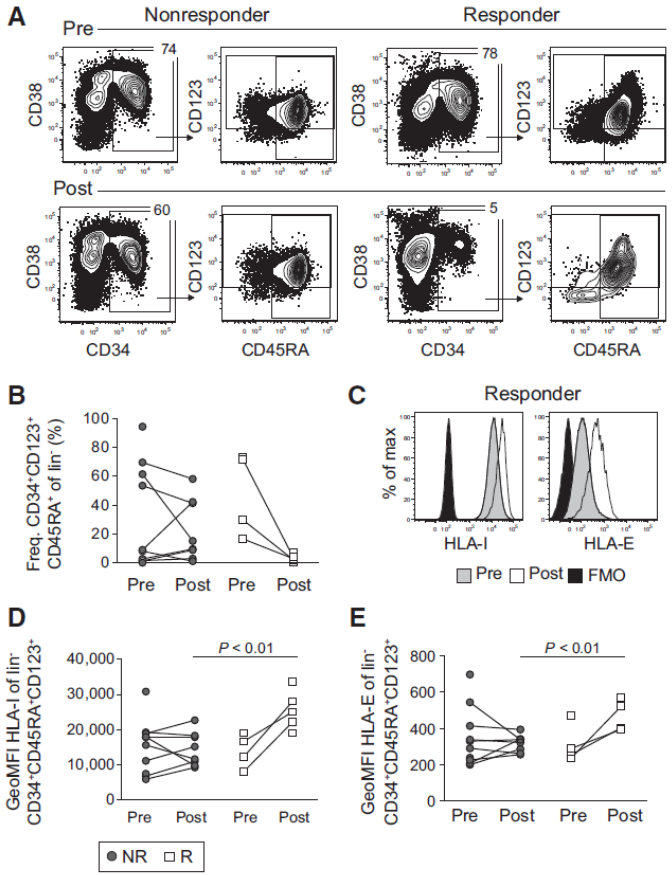
Disease-free Survival



Parisi et al, EHA, 2018

Infused NK cells have immunoediting capacity of leukemia burden and reduce high-risk clones





Bjorklund et al, Clin Cancer Res, 2018

An algorythm for donor selection and cell processing based on NK functional dose

NKAML: A Pilot Study to Determine the Safety and Feasibility of Haploidentical Natural Killer Cell Transplantation in Childhood Acute Myeloid Leukemia

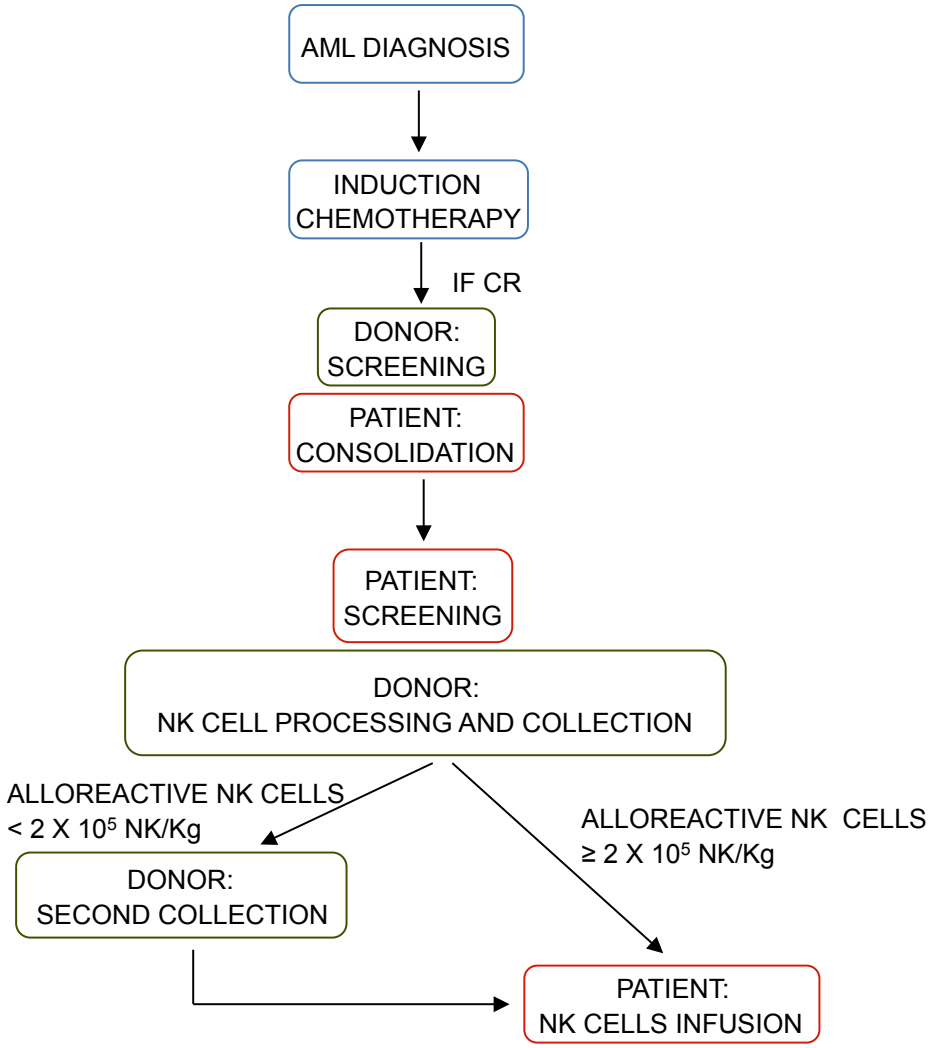
Jeffrey E. Rubnitz, Hiroto Inaba, Raul C. Ribeiro, Stanley Pounds, Barbara Rooney, Teresa Bell, Ching-Hon Pui, and Wing Leung

NK Cell Graft

NK Cells (10^6/kg)	T Cells (10^6/kg)	B Cells (10^6/kg)
38.7	ND	0.106
27.2	ND	1.700
31.1	ND	0.652
37.3	ND	0.148
80.9	ND	0.135
5.2	ND	0.007
7.3	ND	0.004
13.3	0.001	ND
47.7	ND	0.087
13.4	ND	0.082

VOLUME 28 · NUMBER 6 · FEBRUARY 20 2010

JOURNAL OF CLINICAL ONCOLOGY



Lemoli et al, Exp Hematol, 2017

NK-based clinical program

***NKAML**:*

Infusion of alloreactive NK cells as consolidation strategy for adult acute myeloid leukemia patients: a multicenter clinical trial.

ENROLLING

***MRDNK**:*

Infusion of alloreactive NK cells for acute myeloid leukemia patients, eligible for allogeneic stem cell transplantation, with persistent minimal residual disease after conventional chemotherapy.

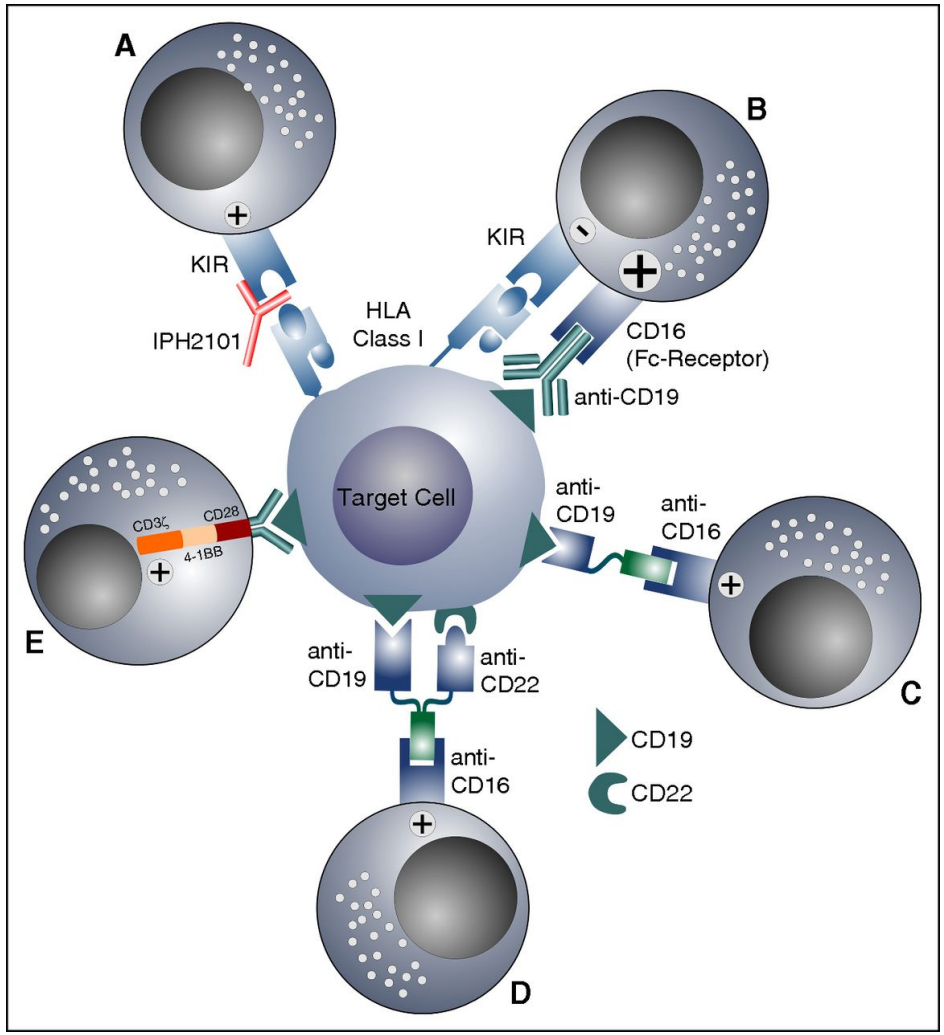
UNDER APPROVAL

Financial Support by Italian Ministry of Health

INFUSION OF ALLOREACTIVE NK CELLS AS CONSOLIDATION STRATEGY FOR ELDERLY ACUTE MYELOID LEUKEMIA PATIENTS: A MULTICENTER CLINICAL STUDY

"NKAML"

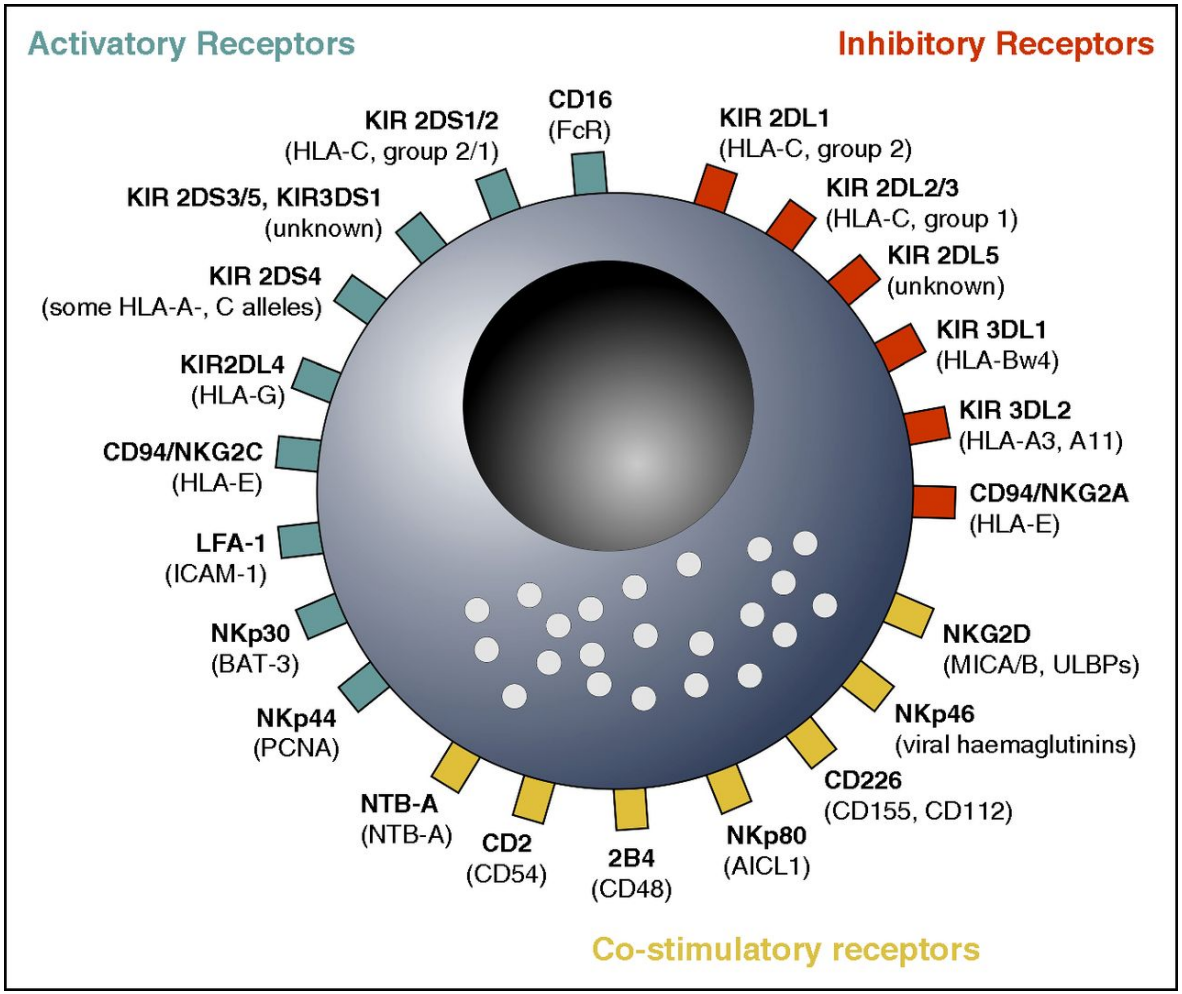
Strategies to overcome the KIR-KIRL-mediated inhibition of NK cells



Handgretinger et al. Blood 2016

- Blocking KIR-KIRL interaction
- Activation of CD16 (Fc-receptor) on NK cells with an antibody directed against leukemic cells
- Bispecific and Trispecific killer engagers activate NK cells via the Fc-receptor against leukemia cells
- CAR-NK cells directed against leukemia antigens

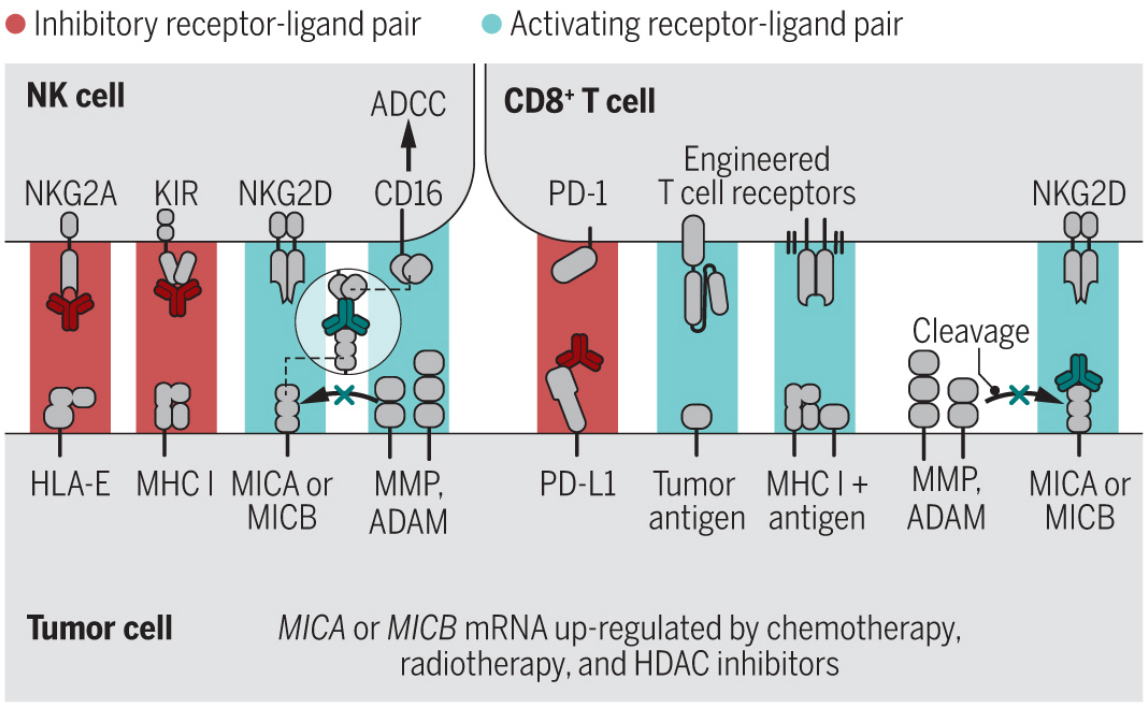
NK cells “naturally” kill cell targets without prior sensitization



Handgretinger et al. Blood 2016

Combinatorial strategies with MICA-MICB mAb

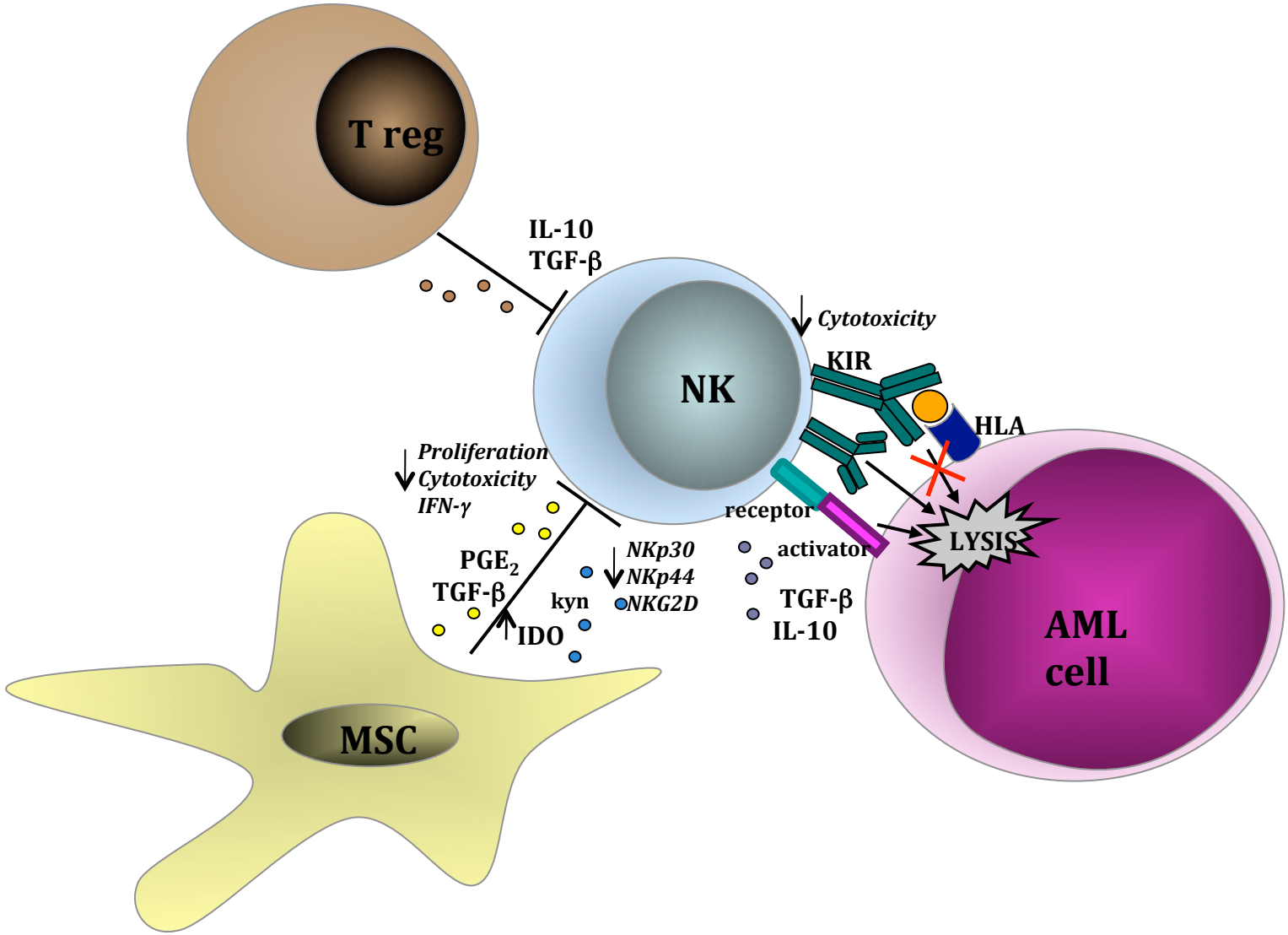
The MICA-MICB mAb stabilizes these NKG2D ligands on tumor cells, inducing tumor cell killing by NK and CD8⁺ T cells. Combinations with immune checkpoint inhibitors (anti–PD-1 or anti–PD-L1), engineered immune cells, or antibodies blocking NKG2A or KIR could amplify antitumor activity. HLA-E, human leukocyte antigen E.



Adelheid Cerwenka, and Lewis L. Lanier Science 2018;359:1460-1461

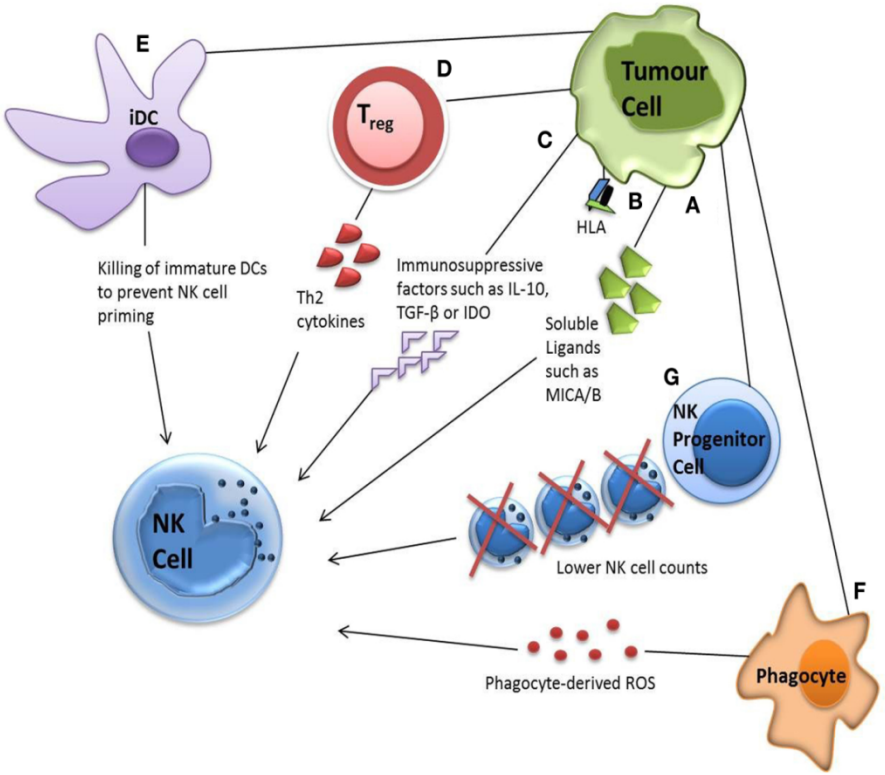
Science
AAAS

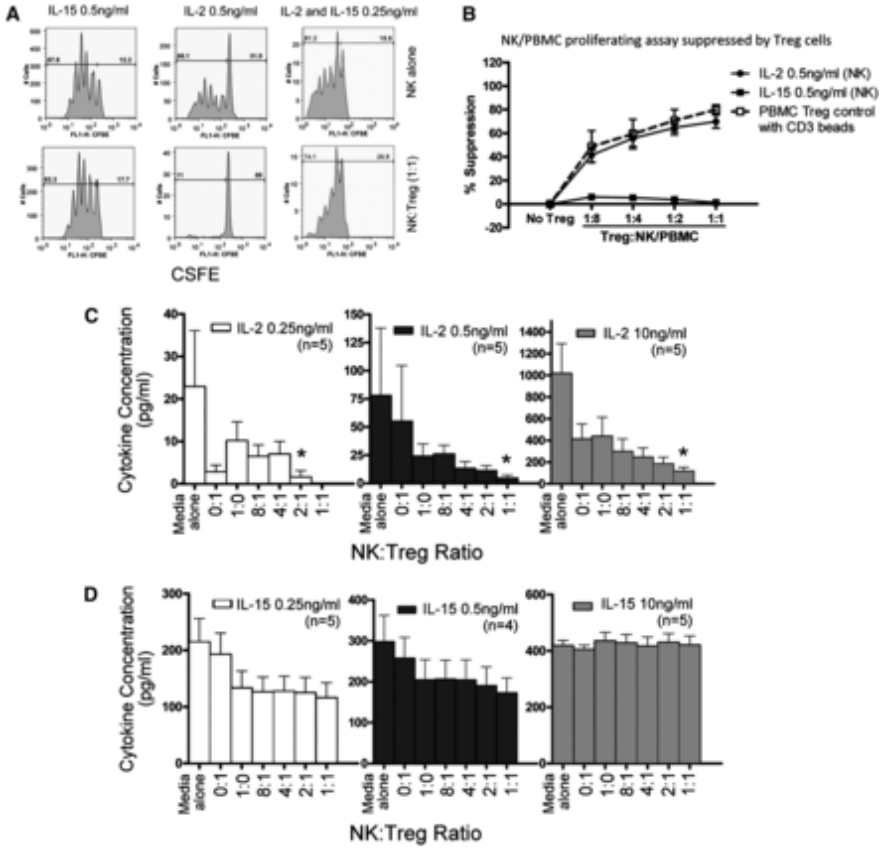
How components of BM microenvironment may inhibit NK activity against AML



Parisi et al, Front Immunol, 2017

Patient-derived factors on alloreactive NK immunotherapy: the role of Tregs



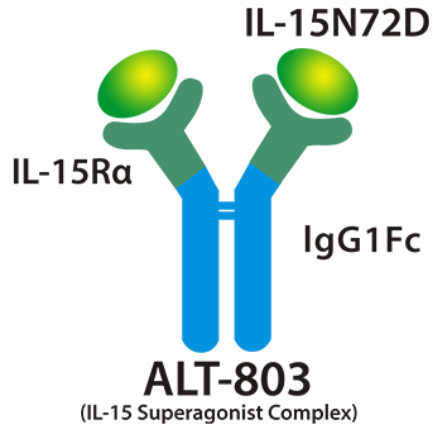


Bachanova et al, Blood, 2014

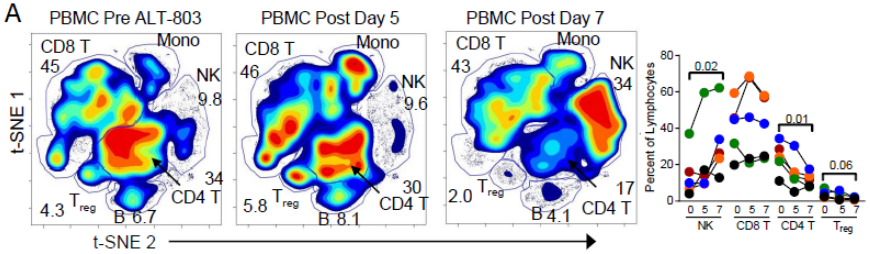
First-in-human Phase 1 Clinical Study of the IL-15 Superagonist Complex ALT-803 to Treat Relapse after Transplantation

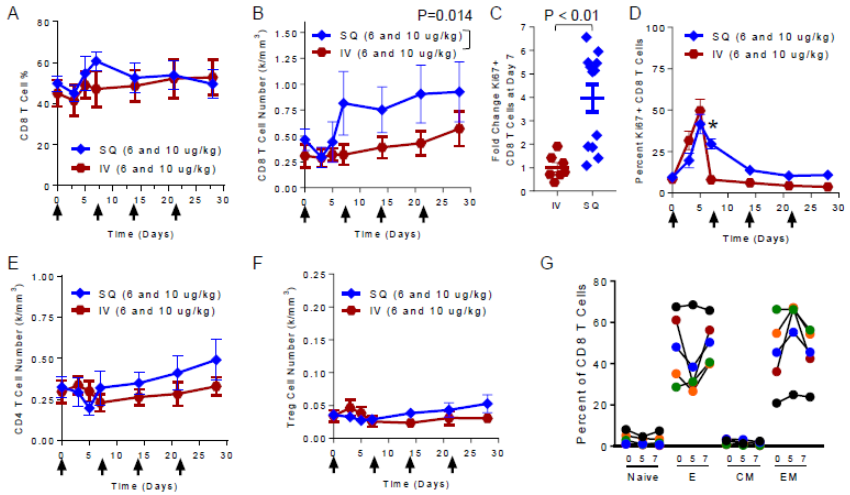
Rizwan Romee, Sarah Cooley, Melissa M. Berrien-Elliott, Peter Westervelt, Michael R. Verneris, John E. Wagner, Daniel J. Weisdorf, Bruce R. Blazar, Celalettin Ustun, Todd E. DeFor, Sithara Vivek, Lindsey Peck, John F. DiPersio, Amanda F. Cashen, Rachel Kyllo, Amy Musiek, András Schaffer, Milan J. Anadkat, Ilana Rosman, Daniel Miller, Jack O. Egan, Emily K. Jeng, Amy Rock, Hing C. Wong, Todd A. Fehniger and Jeffrey S. Miller

blood®



ALT-803 is novel IL-15 superagonist complex consisting of an IL-15 mutant (IL-15N72D) bound to an IL-15 receptor α/IgG1 Fc fusion protein. **ALT-803** has improved pharmacokinetic properties, longer persistence in lymphoid tissues and enhanced anti-tumor activity compared to native, non-complexed IL-15 in vivo.





Prepublished online February 20, 2018;
doi:10.1182/blood-2017-12-823757

Conclusions

- The demonstration of the significant clinical activity of alloreactive purified NK cells outside the transplantation setting is the rationale for exploiting this strategy as adoptive immunotherapy

- The results from early safety studies have clearly paved the way for designing a new generation of efficacy clinical studies

- Biological issues need full elucidation and clinical correlation

- NK alloreactivity may represent the platform for expanding the field to innovative NK cell-based approaches

Acknowledgements

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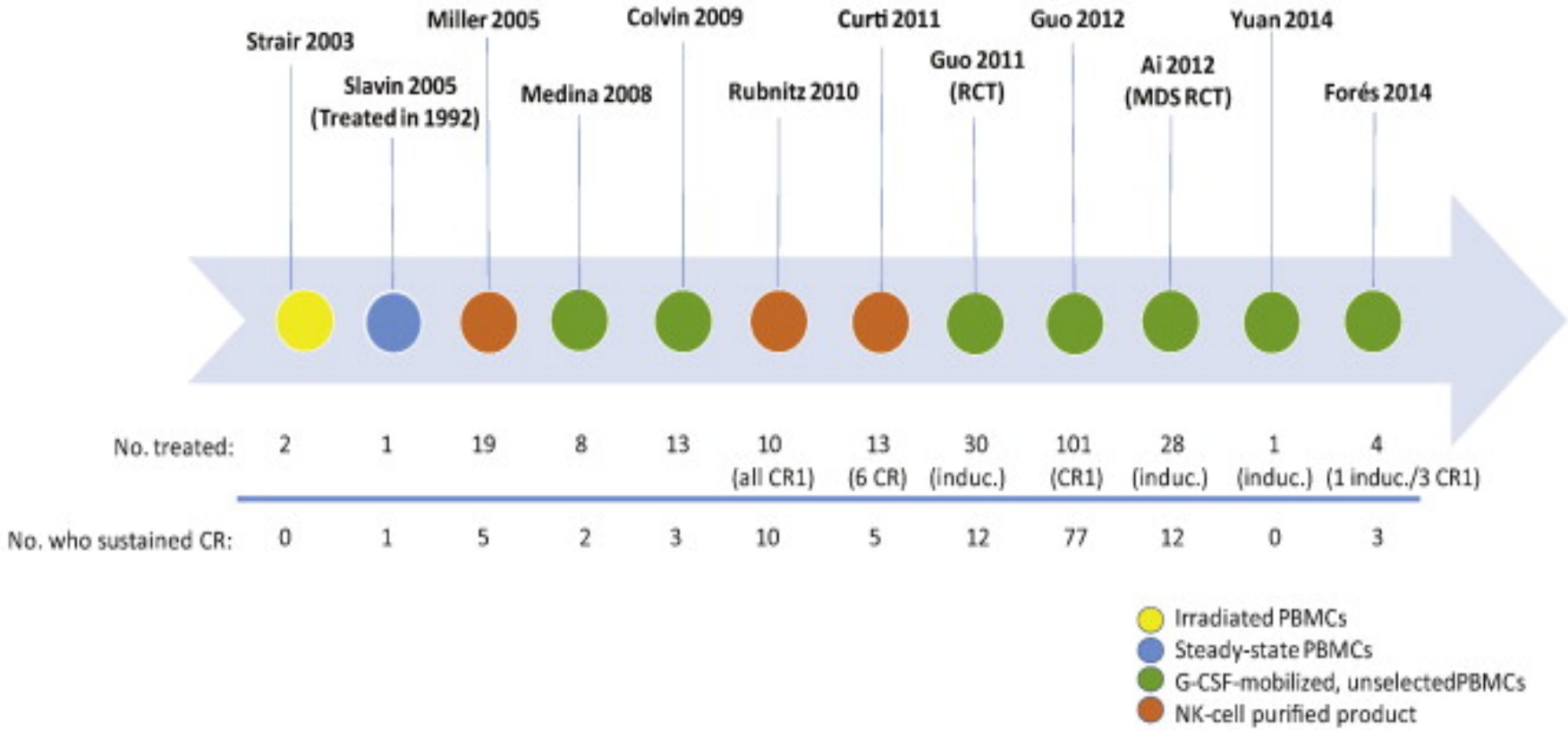
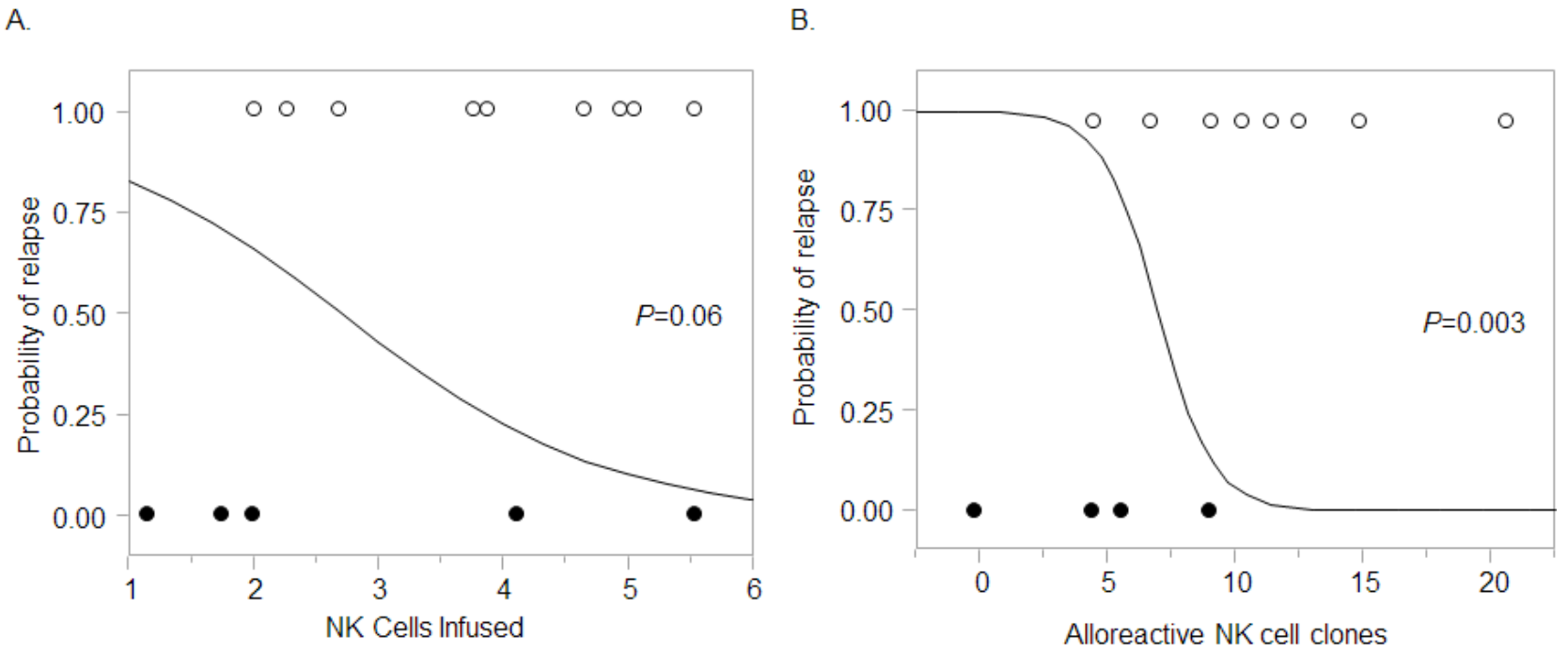
Russell E. Lewis

Time-line summary of alloreactive immunotherapy for AML



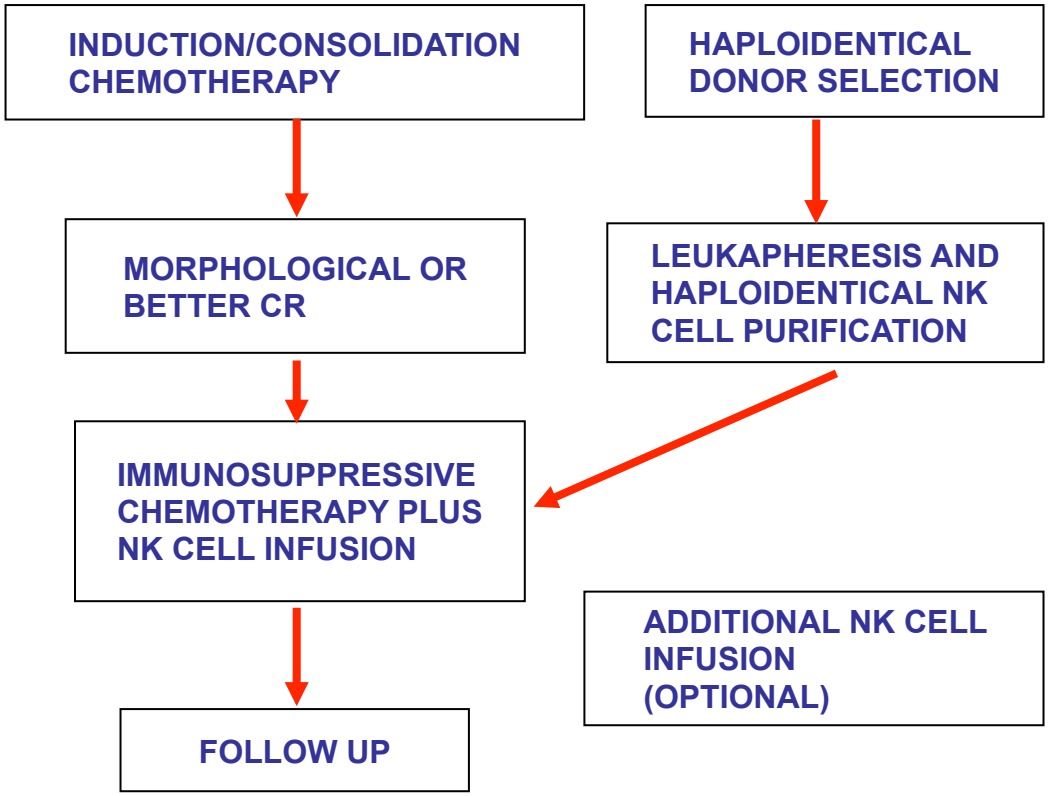
Krakow et al, Blood Reviews, 2014

The percentage of donor alloreactive NK cells correlates with relapse rate



Curti et al, Clin Cancer Res, 2016

Infusion of alloreactive NK cells into AML patients in CR



54 high risk AML patients were screened for the availability of one haploidentical KIR ligand mismatched donor

26 patients (48%) had one suitable donor.

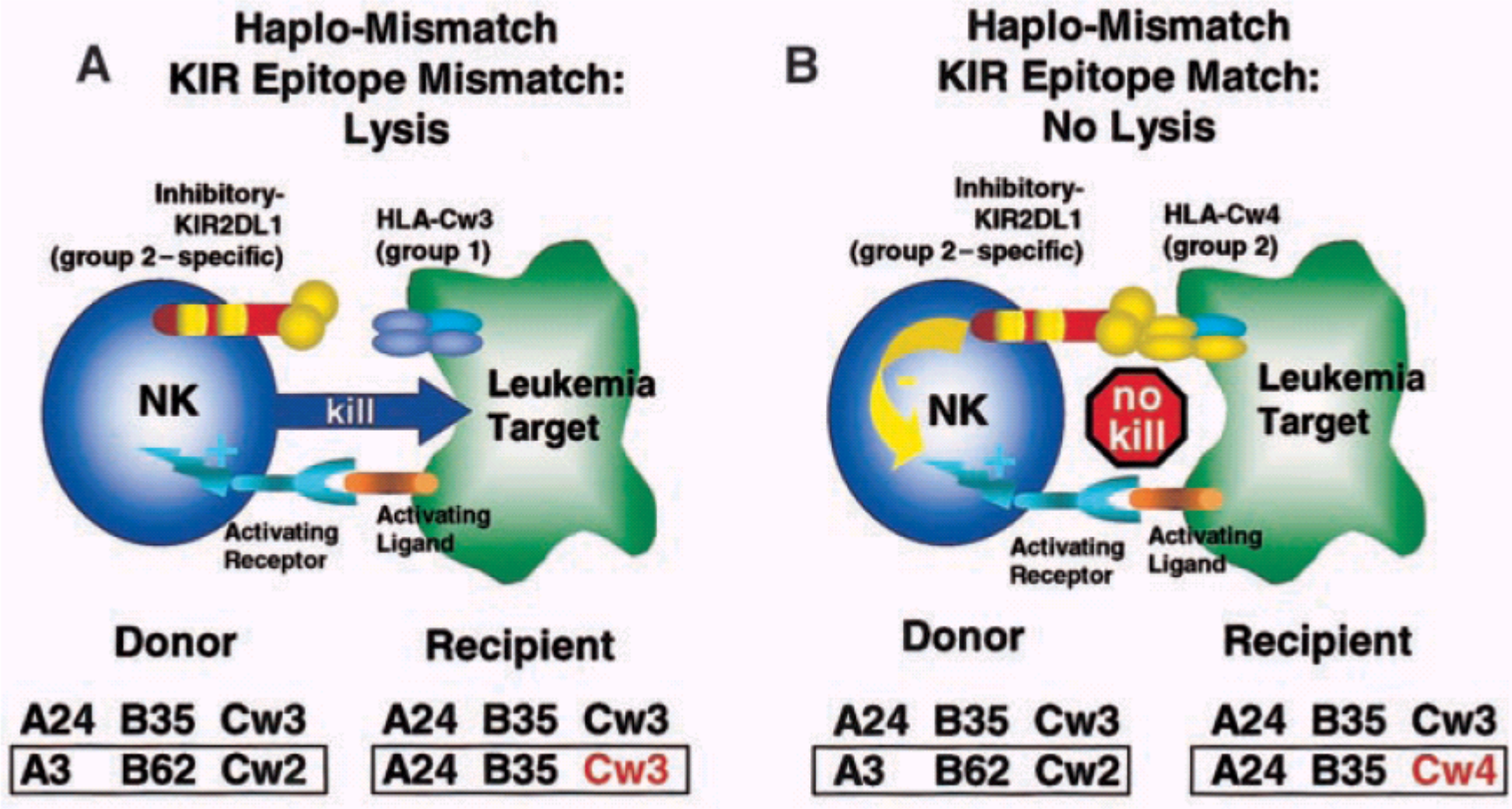
21 patients (38%) infused.

17 patients infused in CR

16 evaluable patients for clinical response

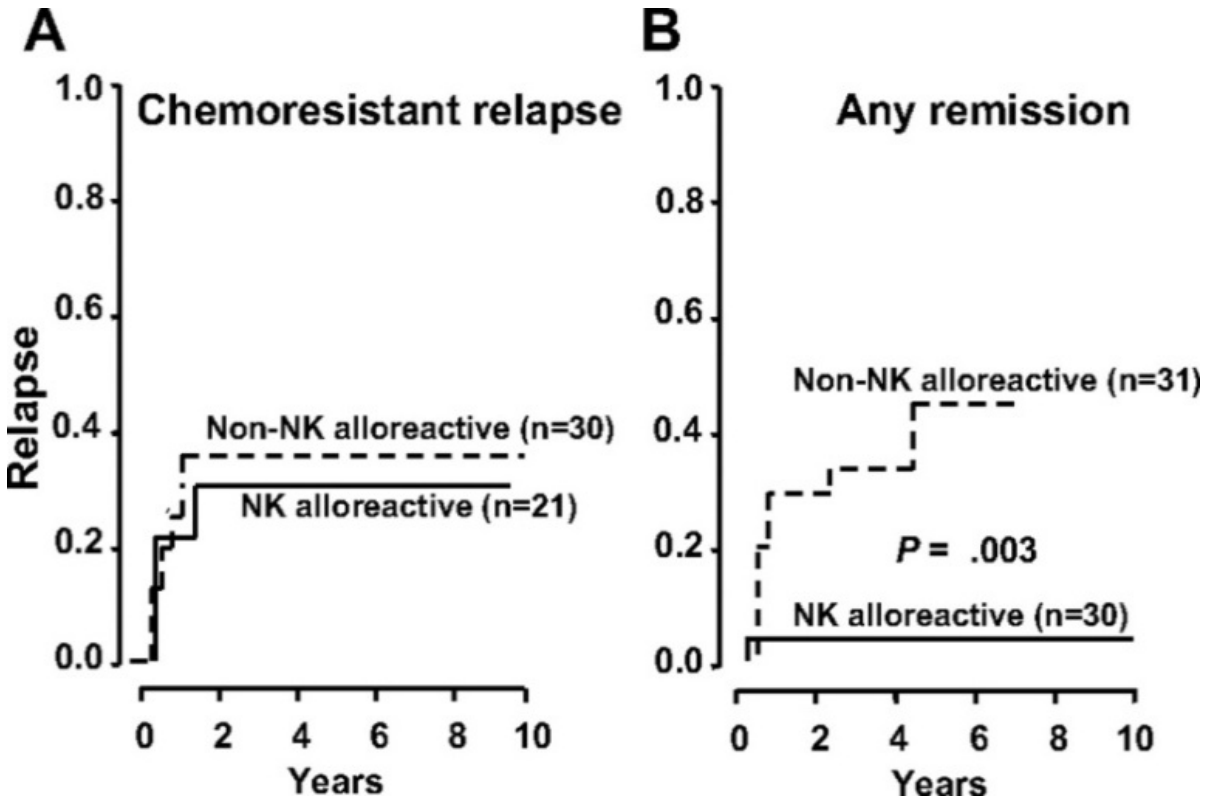
9 CR patients are disease-free after a median follow-up of 27 months

KIR-KIRL mismatch in haploidentical SCT: the missing-self



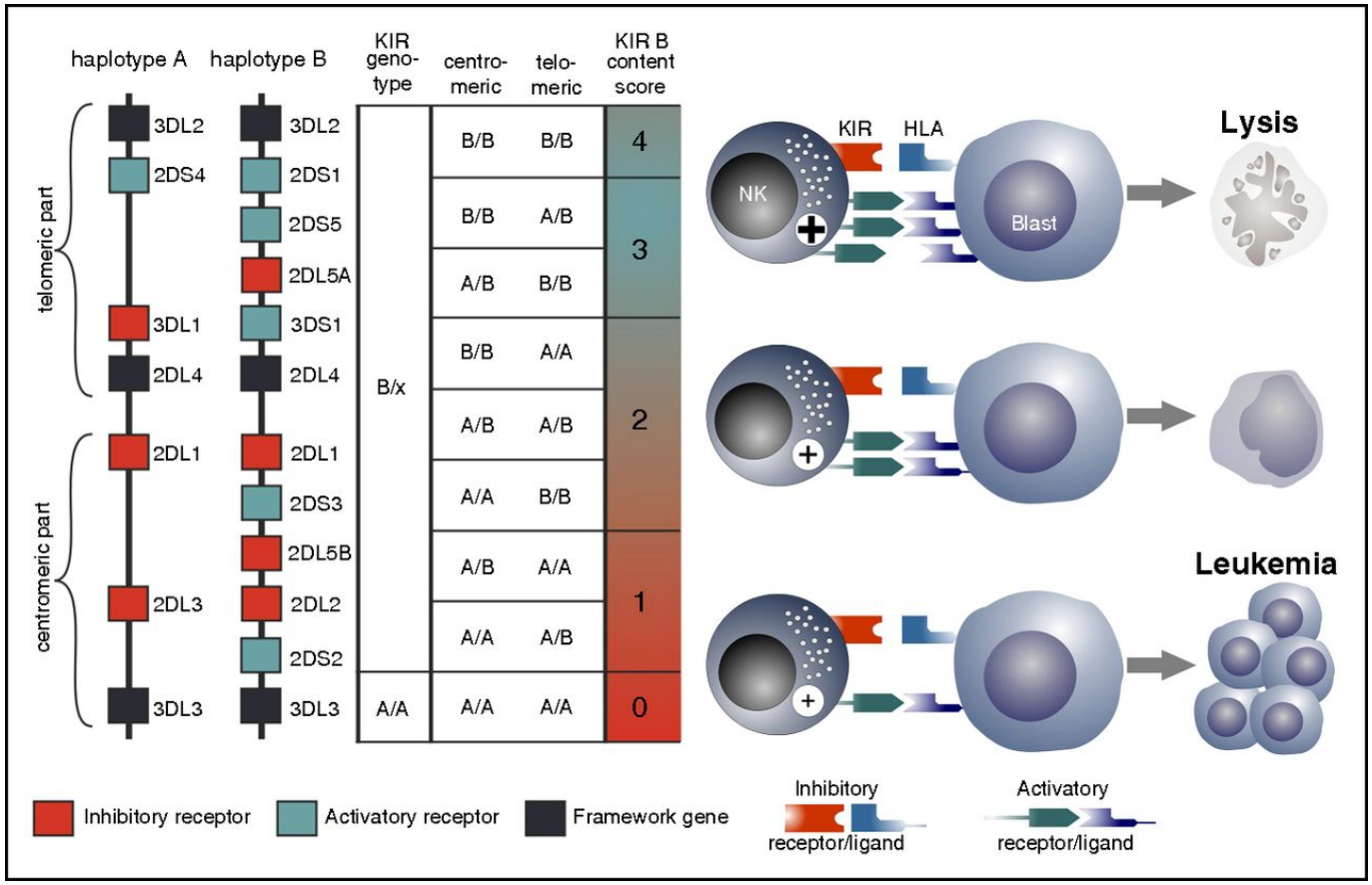
Farag S et al, Blood 2004

Clinical impact of KIR-L mismatch on relapse rate after haploSCT



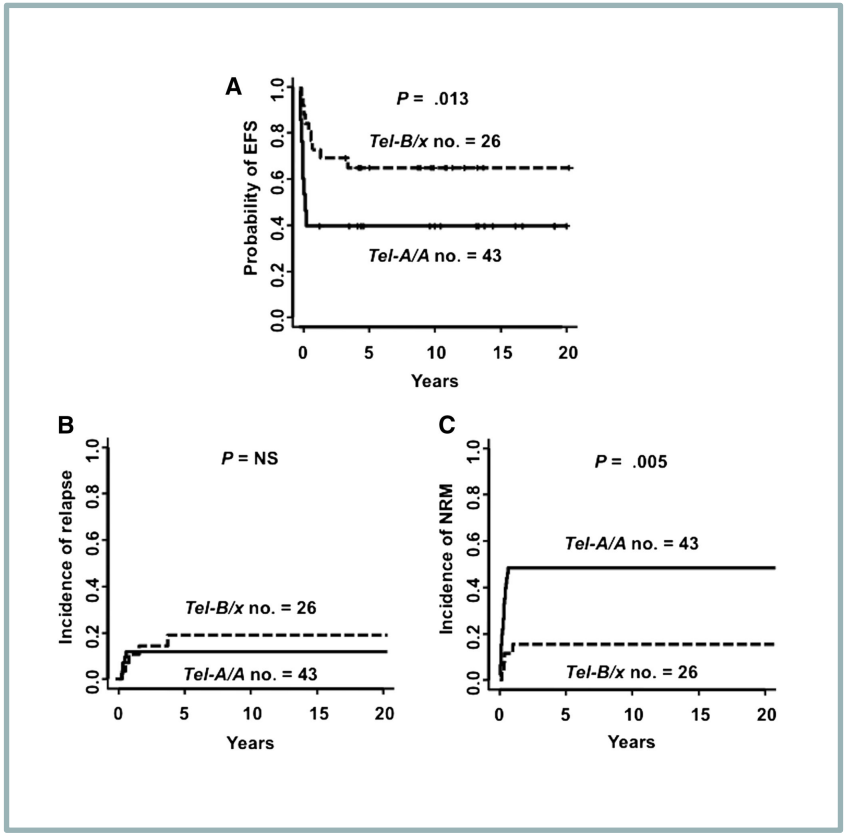
Ruggeri et al, Science 2002; Blood 2007

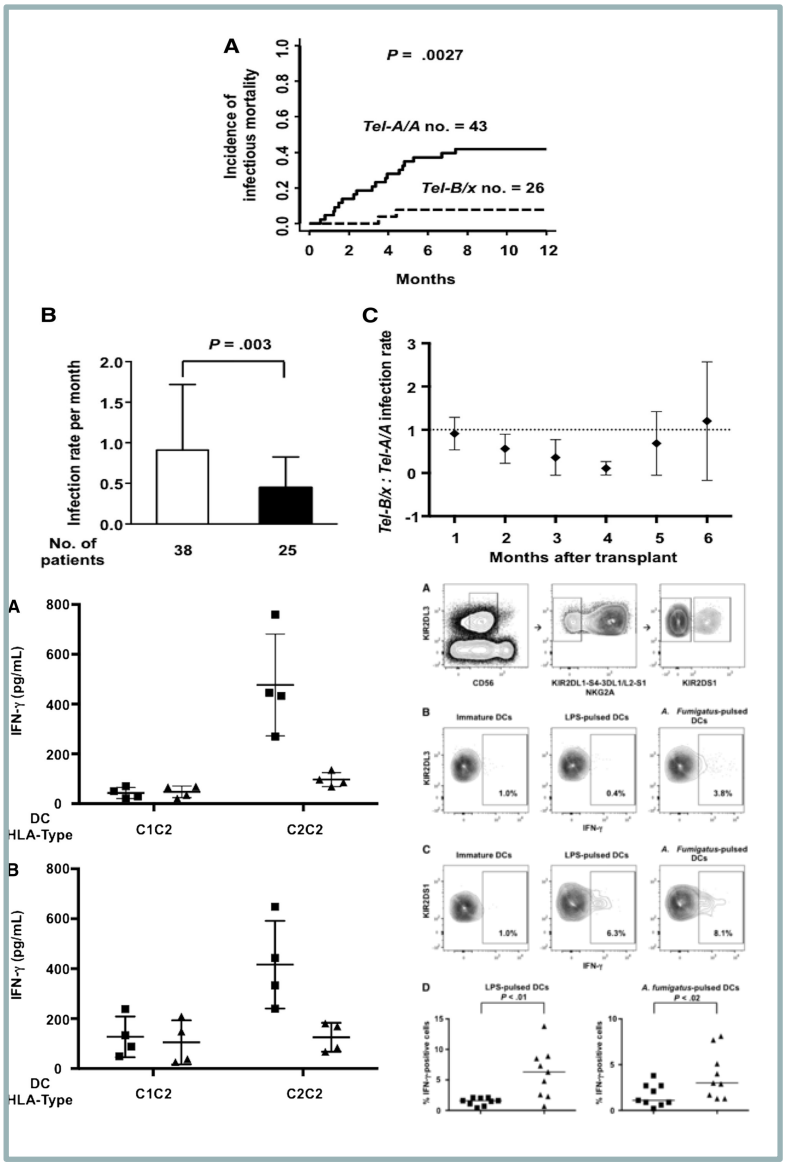
Defining the optimal donor: KIR-L mismatch plus activating KIRs



Handgretinger et al. Blood 2016

KIR-L mismatch and activating KIRS: improved clinical outcome after haploSCT





Mancusi et al. Blood 2015