NK and other ILCs: From bench to bedside

Lorenzo Moretta

Pediatric Hospital Bambino Gesù

Natural killer cell: a major player of the innate immunity

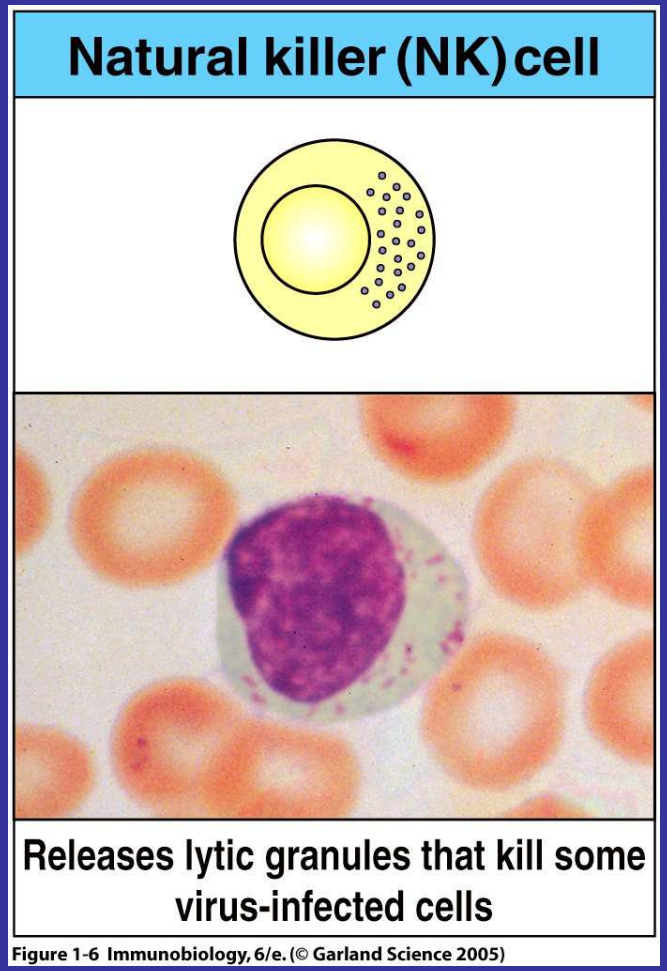
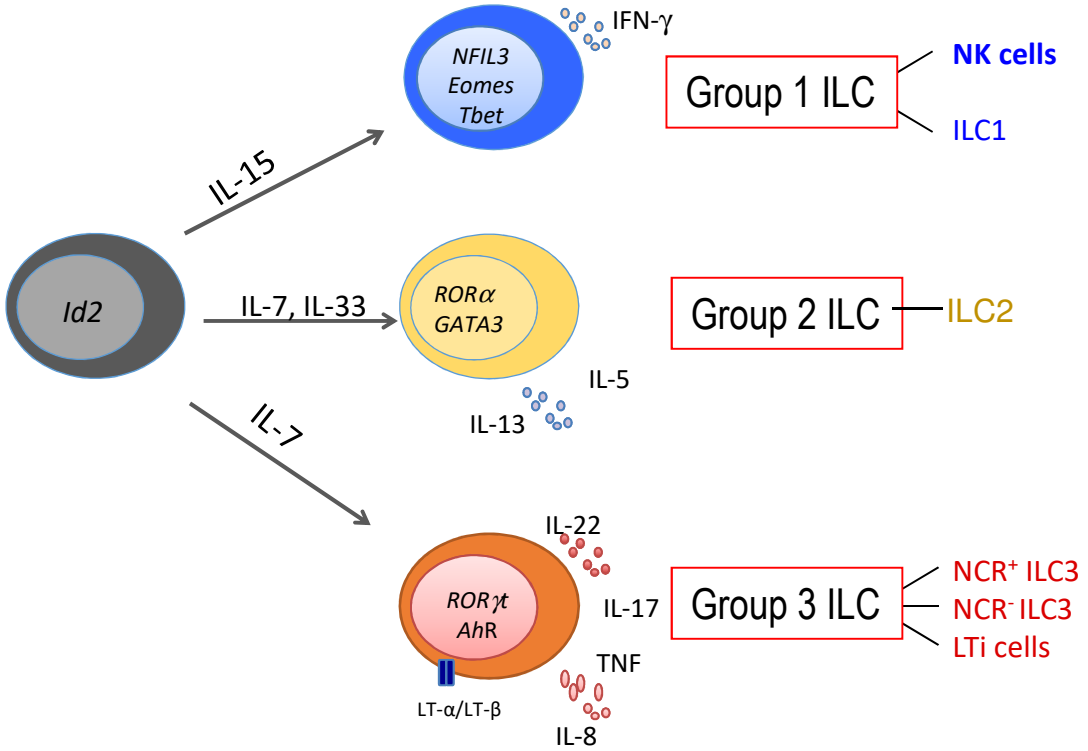


Figure 1-6 Immunobiology, 6/e. (© Garland Science 2005)

Cells of the innate immunity:
«the unsung heroes».

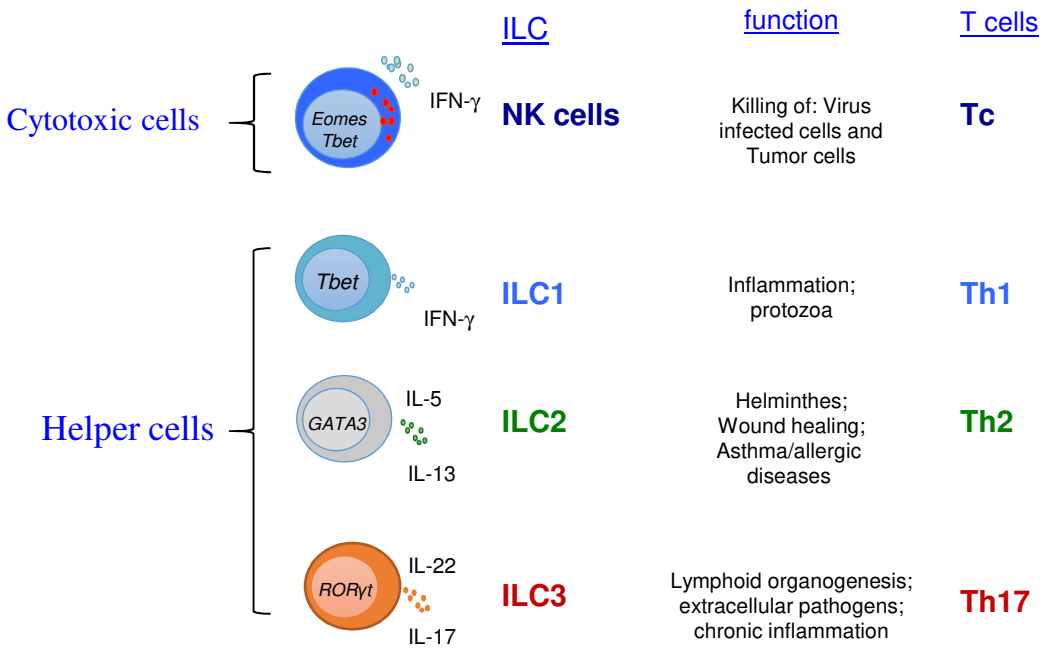
(Peter Parham)

Innate Lymphoid Cells (ILC)



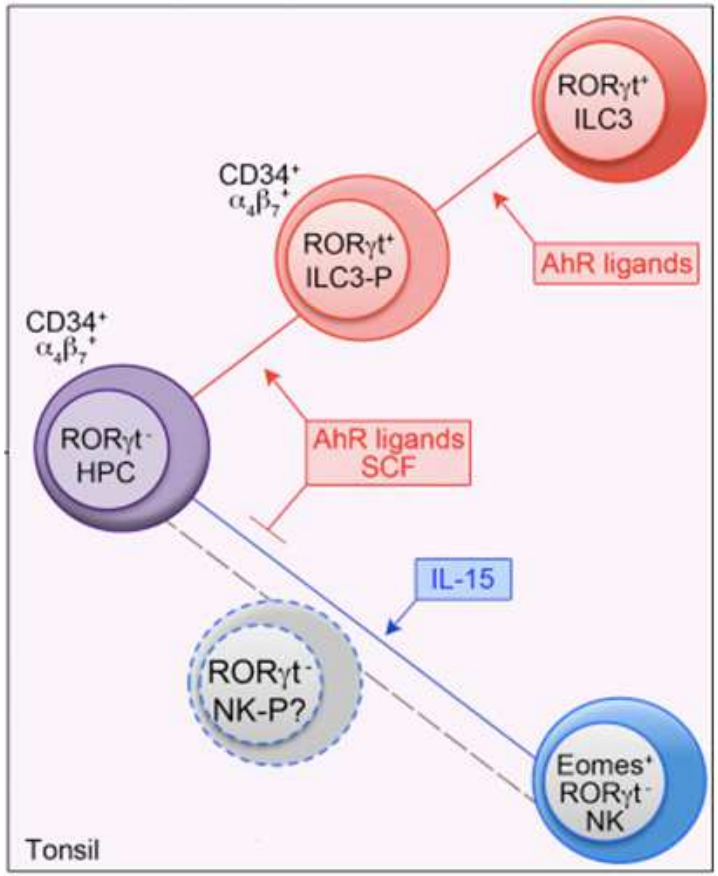
Common features of Innate and adaptive lymphoid cells

The developmental, transcriptional, and effector programs of ILCs mirror those of T lymphocytes:



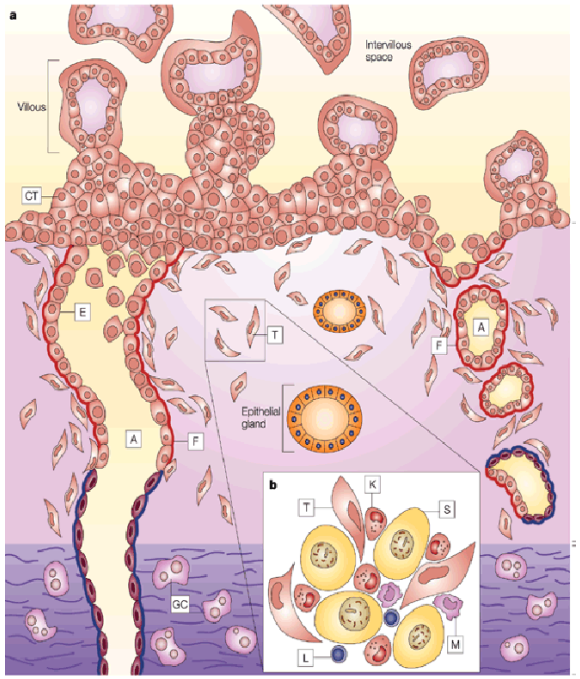
Committed Lymphoid Precursors (CLP) giving rise to ILC are present in different tissues

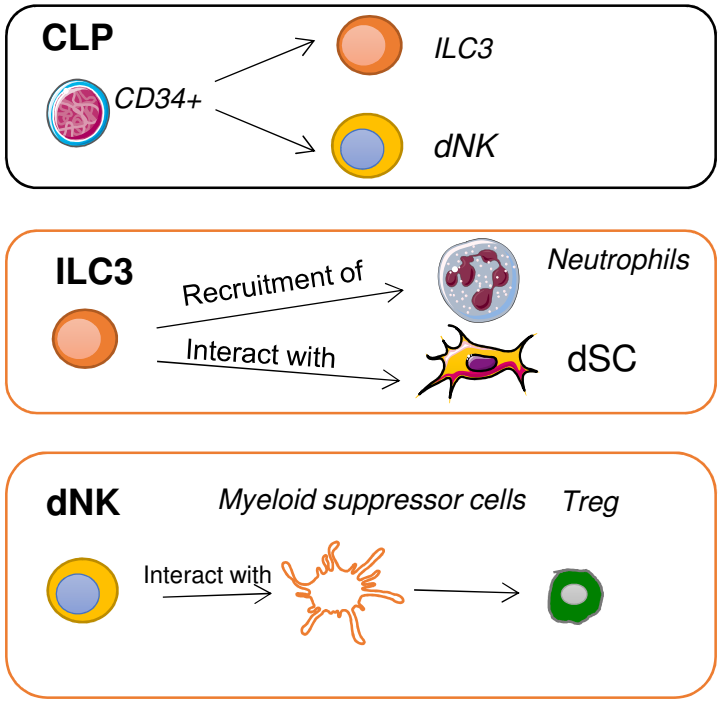
Committed lymphoid Precursors (CLP) are present in Tonsils.



Montaldo E. et al. Immunity. 2014

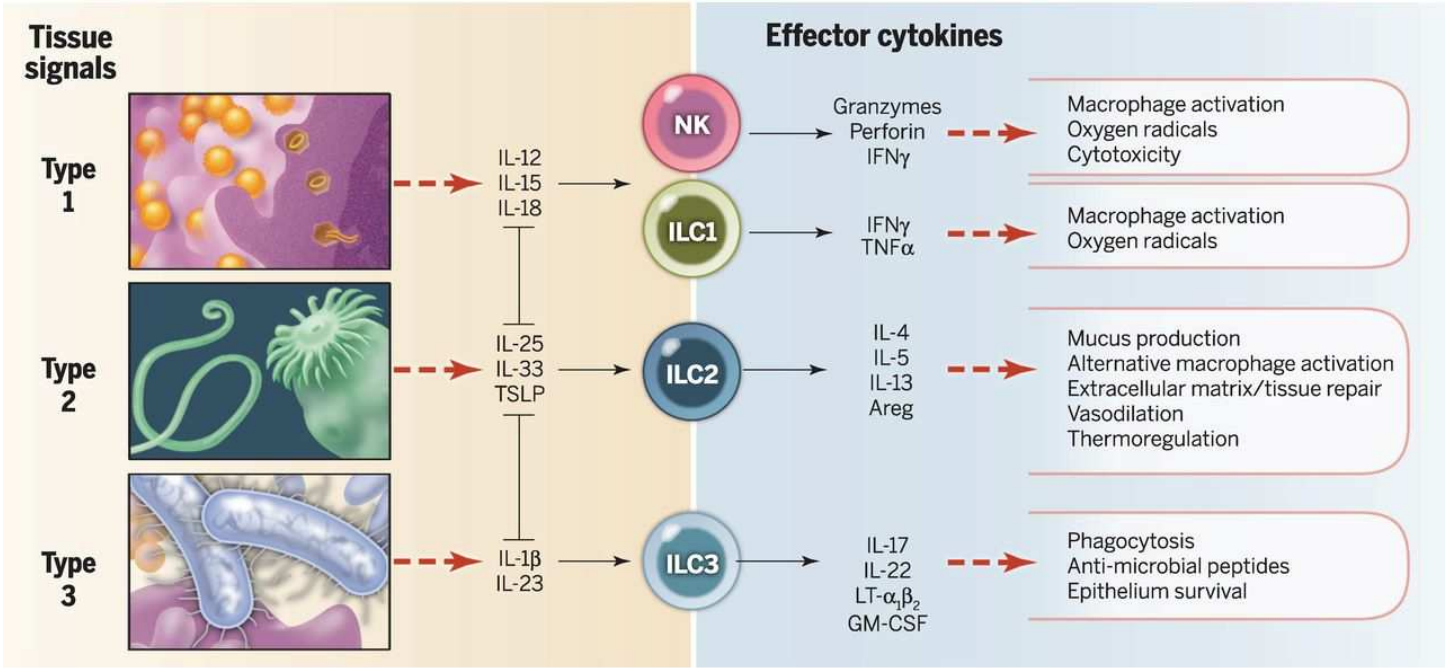
Presence of Committed Lymphoid Cell Precursors (CLP) in different tissues: the decidua case





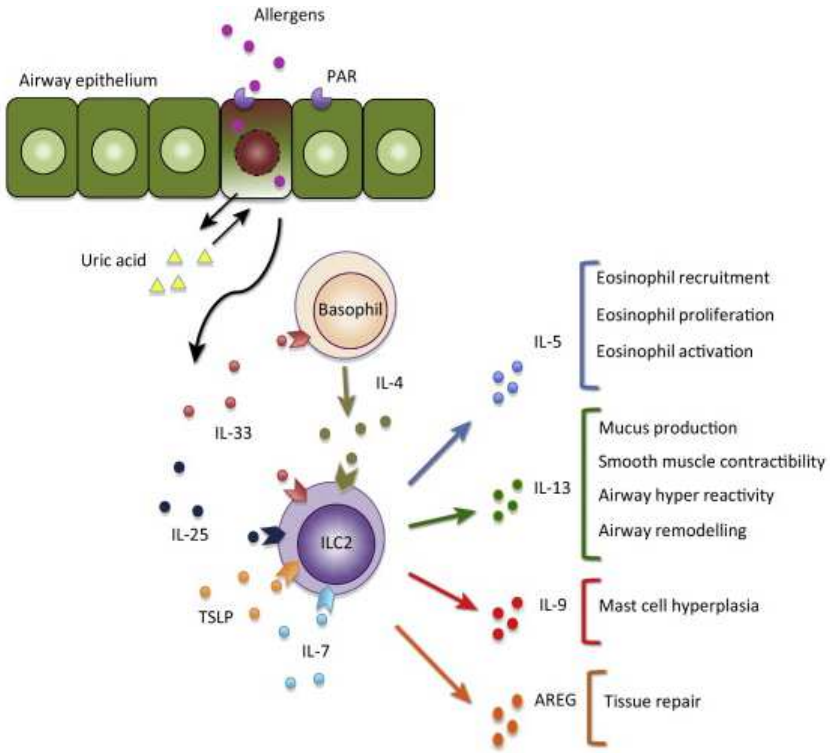
Vacca P. et al. Mucosal Imm. 2015
Croxatto D. et al. Mucosal Imm. 2016

Signals from injured or infected tissues expand and activate NK cells, ILC1s, ILC2s, and ILC3s.



Eberl et al. Science 2015

ILC2-induced allergic responses

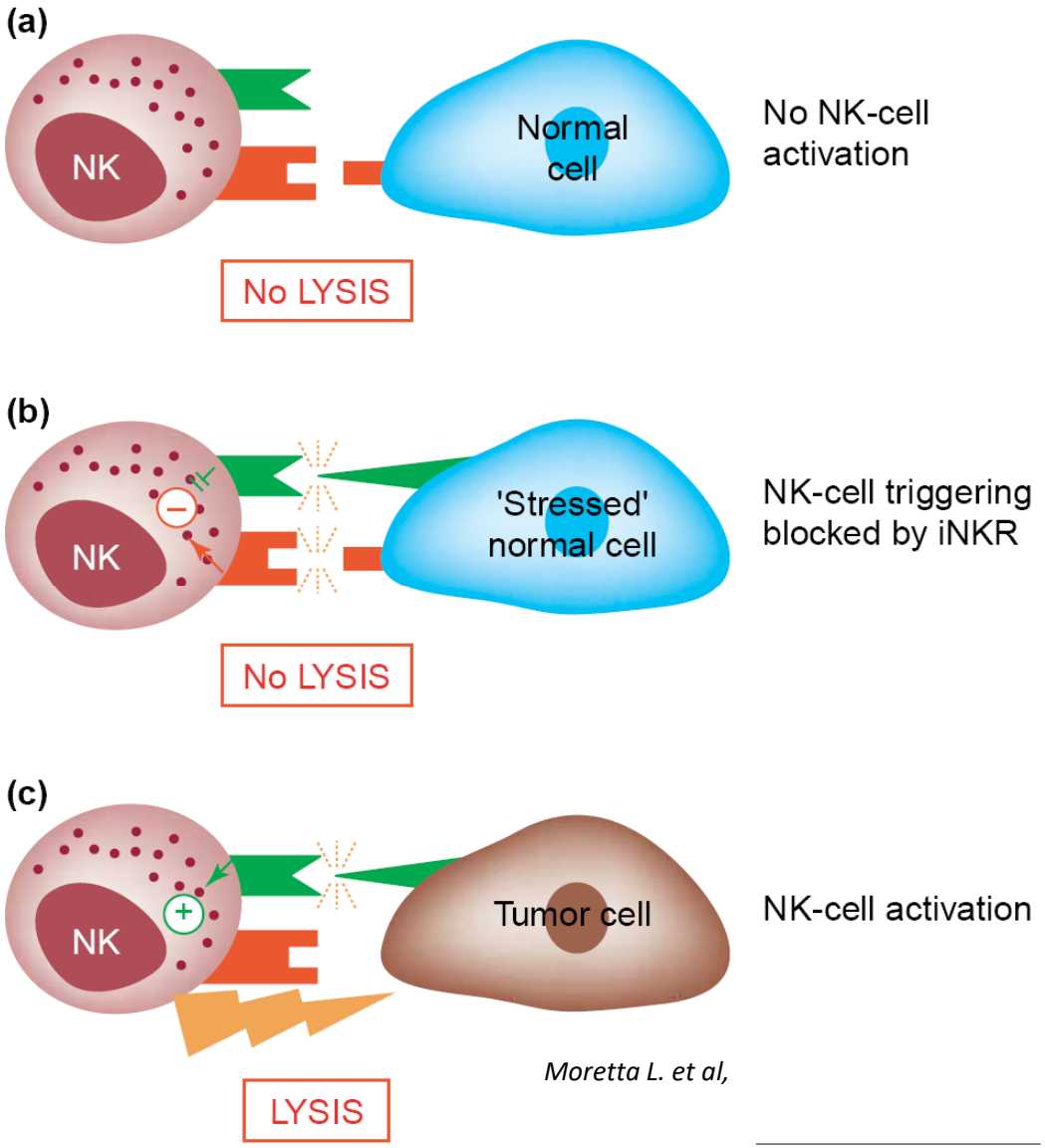


Stimulation of group 2 ILCs by epithelium-derived cytokines leads to innate type 2 immunity

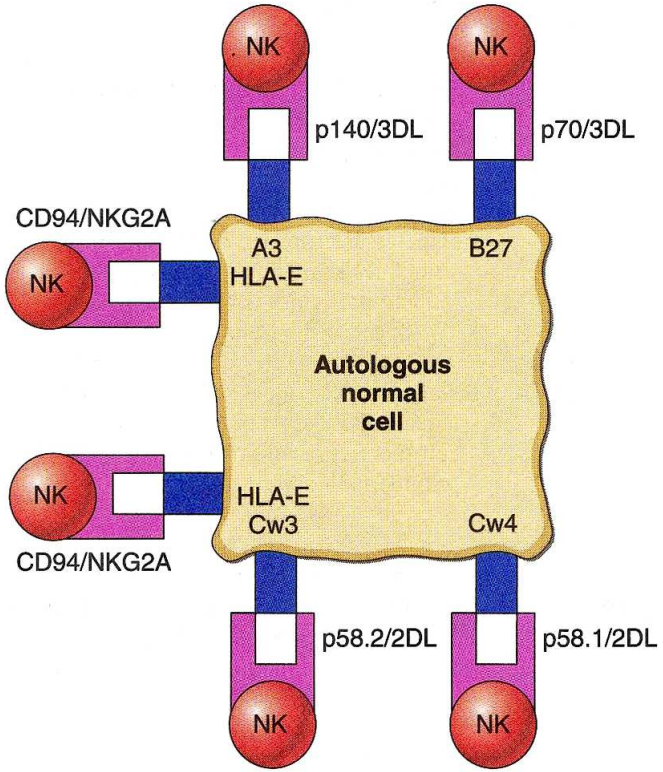
NK cell functions

- **Cytotoxicity**
  - Tumor or leukemia cell killing
  - Killing of virus infected cells
  - DC editing
  - ADCC
- **Cytokine production**
  - Induction of inflammatory responses
  - Regulation of adaptive immune responses
  - Regulation of hematopoiesis
  - Induction of DC maturation
  - Remodelling of decidual vessels/tissues and
  - Treg induction during pregnancy
- **Proliferation**
- **Memory ?**

Schematic representation of the main interactions occurring between normal natural killer (NK) cells (expressing both HLA class I-specific inhibitory receptors and activating receptors) and potential target cells.

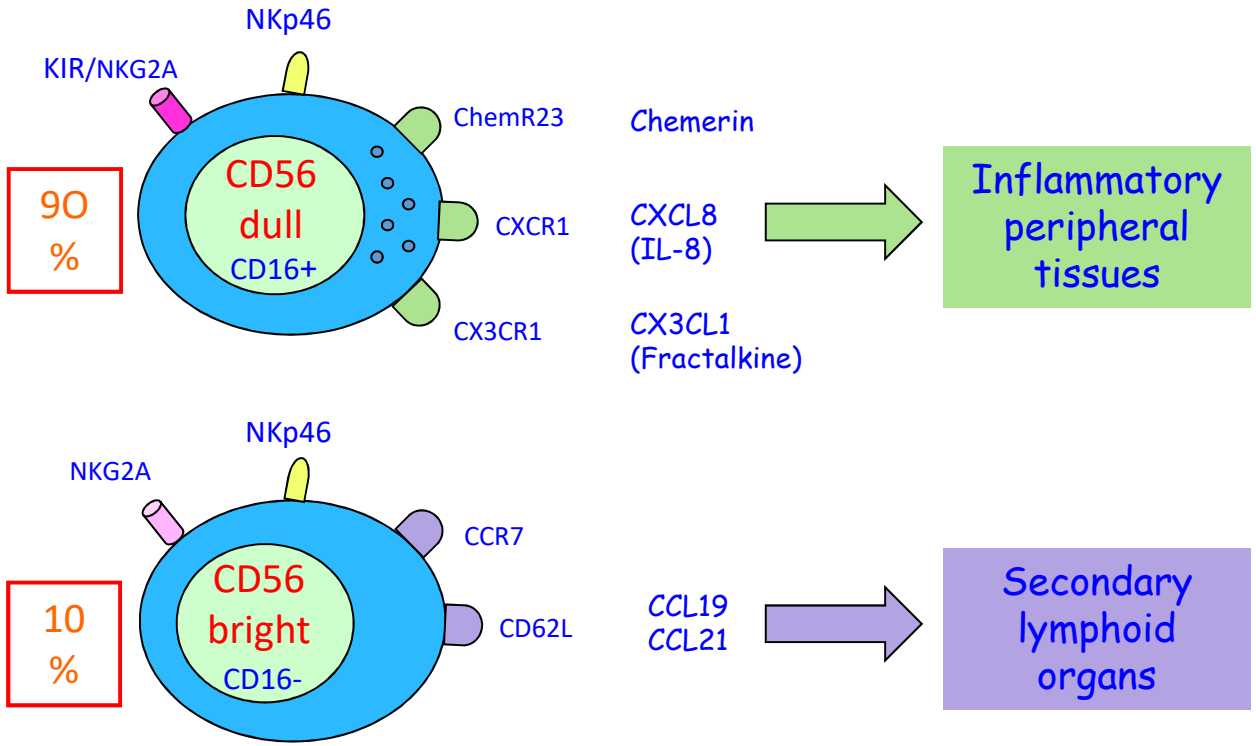


A schematic representation of the human natural killer (NK) receptor repertoire (autologous setting)

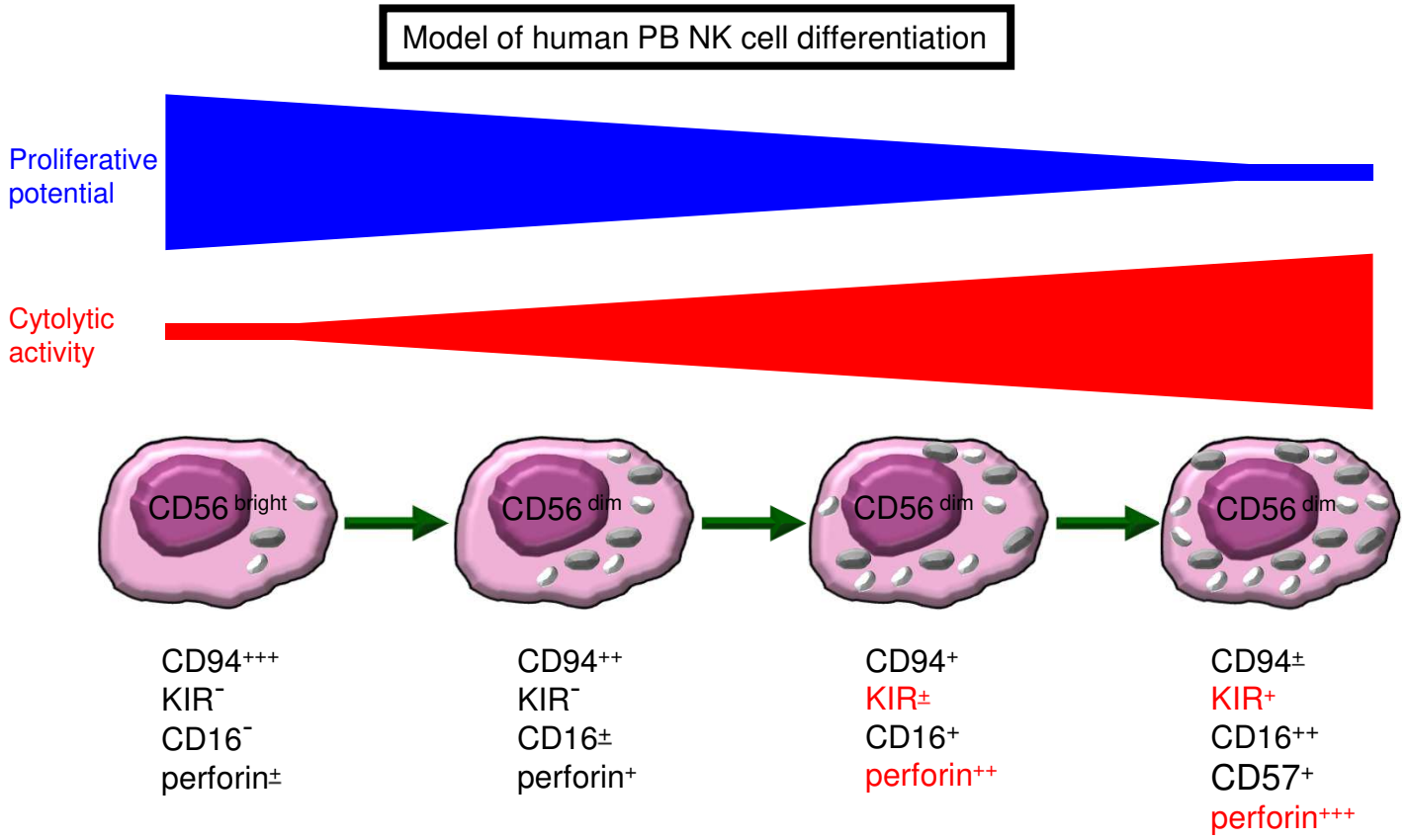


Harrison's 16th edition
Principles of Internal Medicine
(Adapted from Moretta A et al, with permission)

NK cell subsets in human peripheral blood



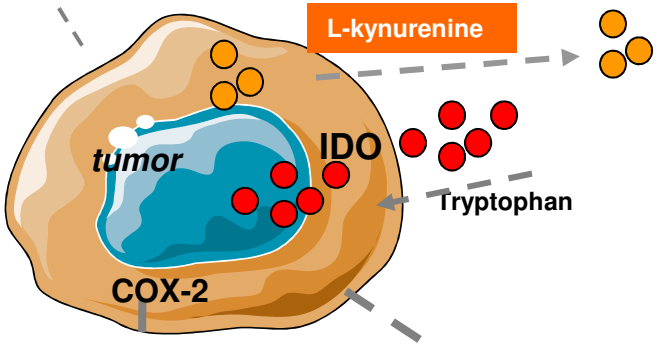
Parolini/Marcenaro et al. Blood 2007
Moretta A et al. Cell Death and Diff 2008



Moretta L, Blood 2010

Effect of the tumor microenvironment on NK cell function

Tumor-derived **immunosuppressive factors**



MIF

Downregulation of NKG2D on NK cells
Krockenberger et al, JI, 2008

- **Downregulation of NKp46 and NKG2D on NK cells**
(Della Chiesa et al, PNAS, 2006)

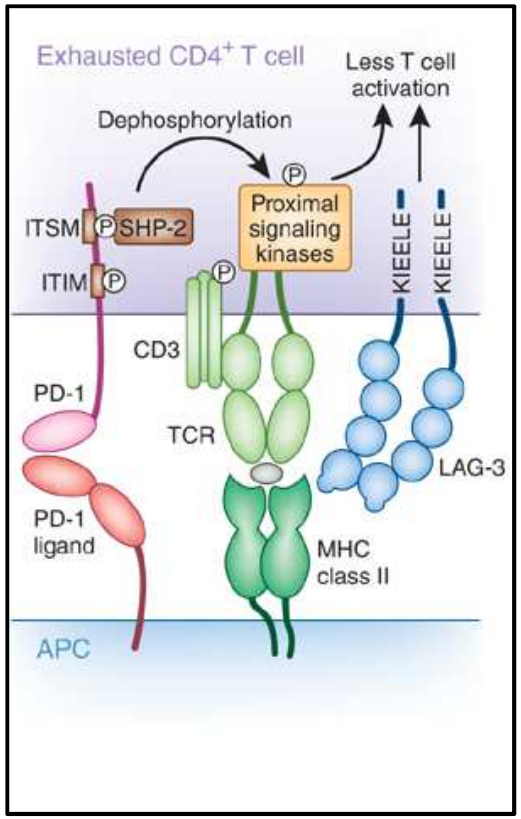
TGF-β

Downregulation of NKp30 and NKG2D on NK cells
Castriconi et al, PNAS, 2003

PGE2

Downregulation of NKp30 and NKp44 on NK cells
Balsamo et al, PNAS, 2009

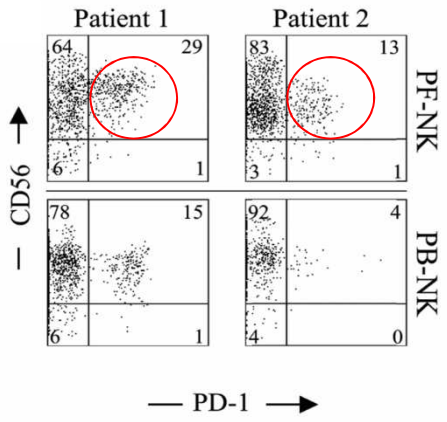
IDENTIFICATION OF A SUBSET OF HUMAN NK CELLS EXPRESSING HIGH LEVELS OF PD-1 RECEPTOR



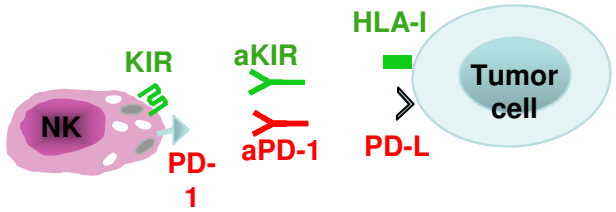
Freeman G.J and Sharpe A.H. Nat.Immunol.2012

Tasuku Honjo (EMBO J 1992 , Immunity 1999)

PD-1⁺ NK cells are enriched in peritoneal fluid/ascites (PF) and PB from ovarian-carcinoma patients



PD-1⁺ NK cells display impaired anti-tumor responses



Restoration of anti-tumor NK activity by the combined use of anti-KIRs and anti-PD-1 mAbs

Pesce et al., JACI 2016

Role of NK cells in Haemopoietic stem cell transplantation for the therapy of high risk leukemias

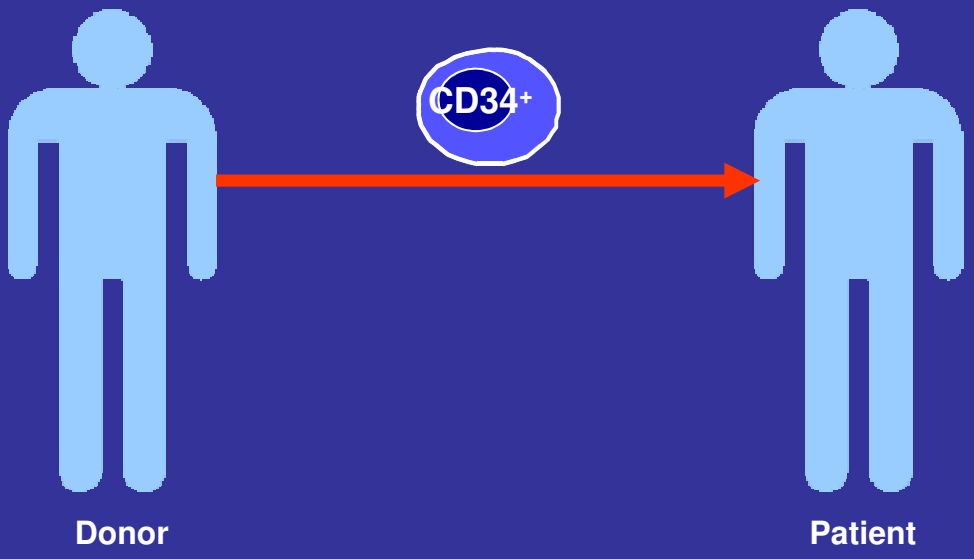
T-depleted haploidentical HSC transplantation

- Only one of the HLA-carrying chromosomes is matched with that of the patient while the other is mismatched (this occurs with parents and 50% of the siblings of the patient)

- KIR/HLA-class I mismatch **in the donor vs recipient direction** may or may not occur

Reisner et al, Blood,1983

Aversa et al, Blood, 1994
Aversa et al, N Engl J Med,1998

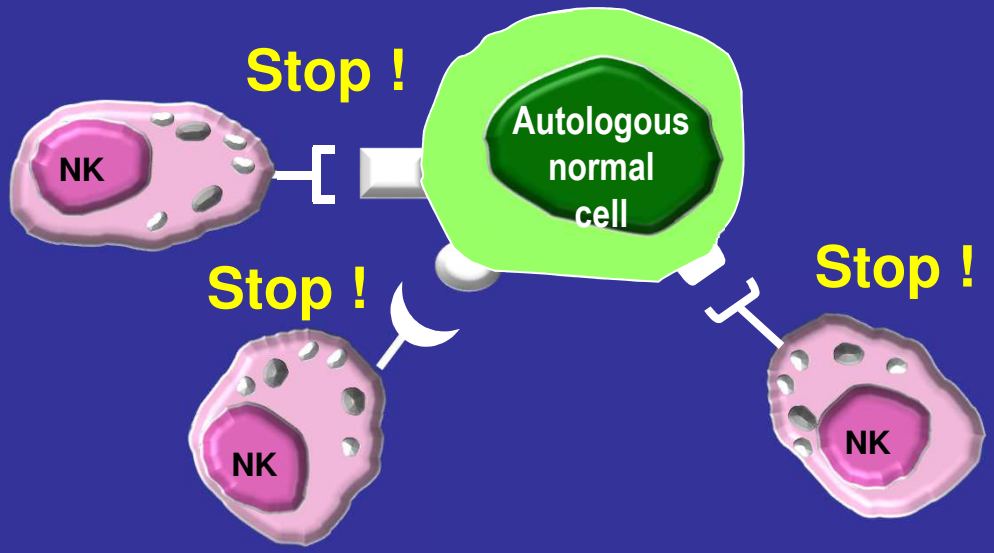


Infusion of highly purified HSC

Coll. F. Locatelli, IRCCS Bambino Gesù

Human NK cells
Autologous setting

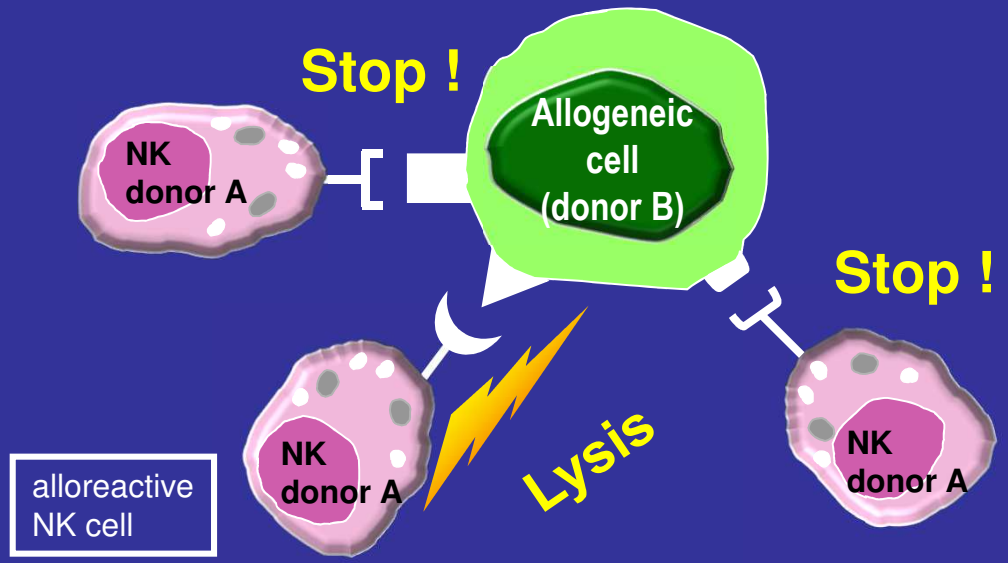
In an autologous setting virtually **all NK cells express receptors that are engaged by self HLA-CII molecules**



Moretta A. et al, J Exp Med 1990 and 1993

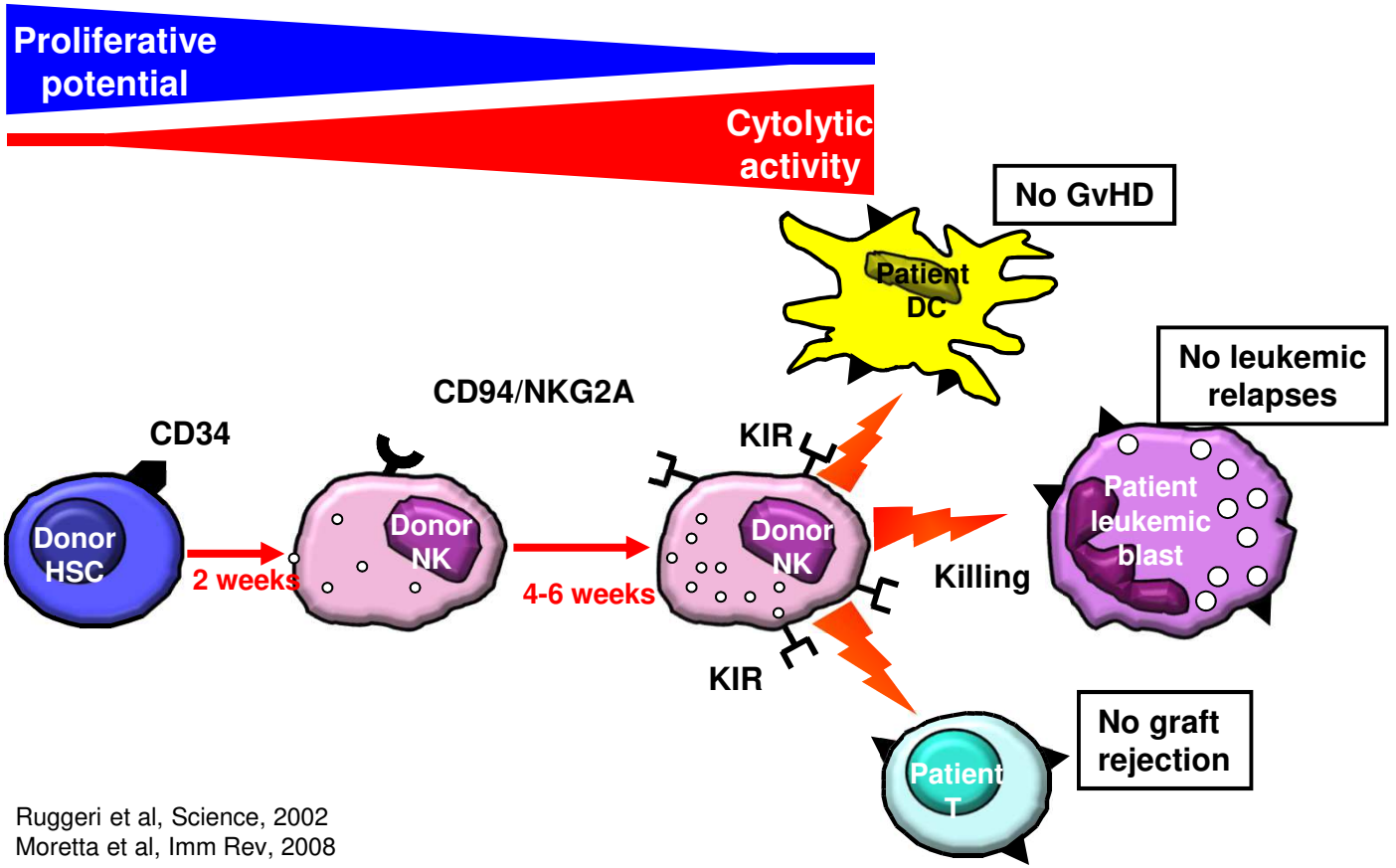
Human NK cells
Allogeneic setting

In an allogeneic setting **a fraction of donor A NK cells may express KIR that are not engaged by the HLA-Cl I alleles of donor B (Alloreactive NK cells)**



Moretta A. et al, J Exp Med 1990 and 1993

Generation of alloreactive NK cells and their therapeutic role in haploidentical hemopoietic stem cell transplantation

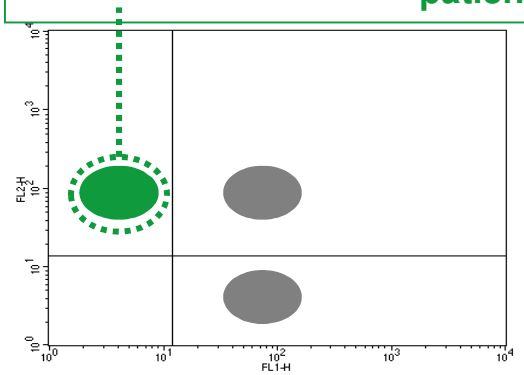


Ruggeri et al, Science, 2002
Moretta et al, Imm Rev, 2008

Definition of the alloreactive NK cell subset in Donor's NK cell population in GvH direction

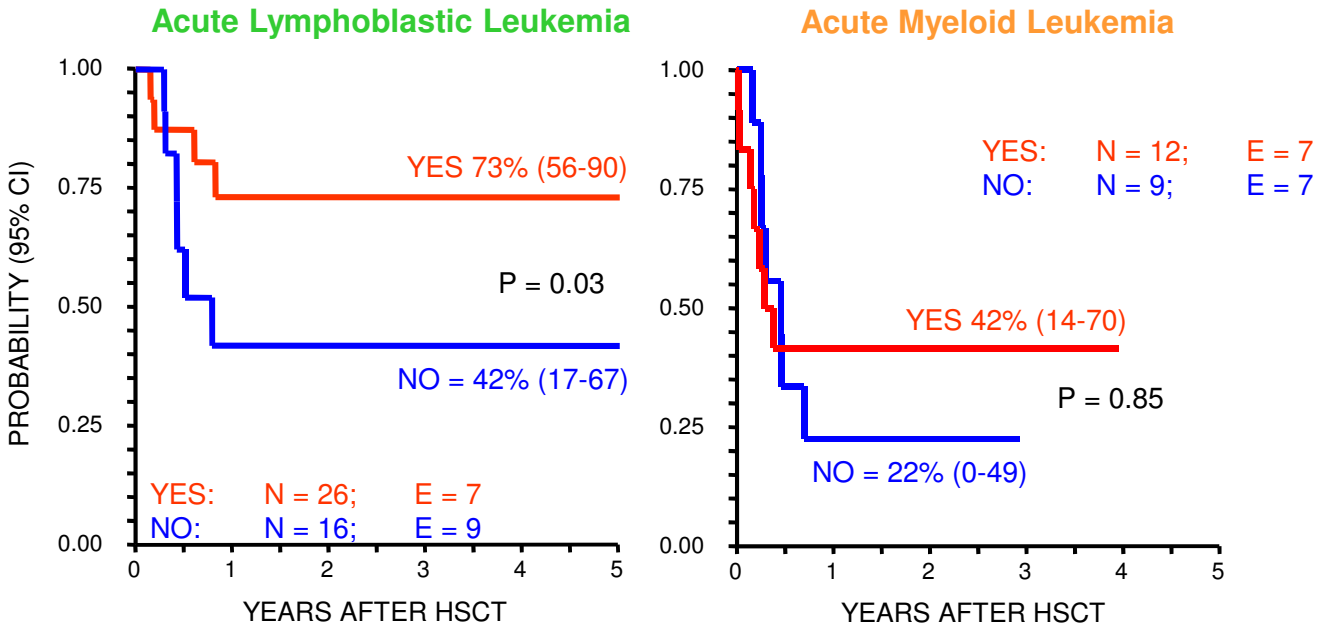
Double fluorescence analysis, using appropriate mAbs combinations, reveals the size of the alloreactive NK cell population (i.e. expressing only KIR that do not recognize HLA-class I alleles of the patient)

KIR specific for HLA-class I alleles absent in patient's haplotype + Activating KIRs



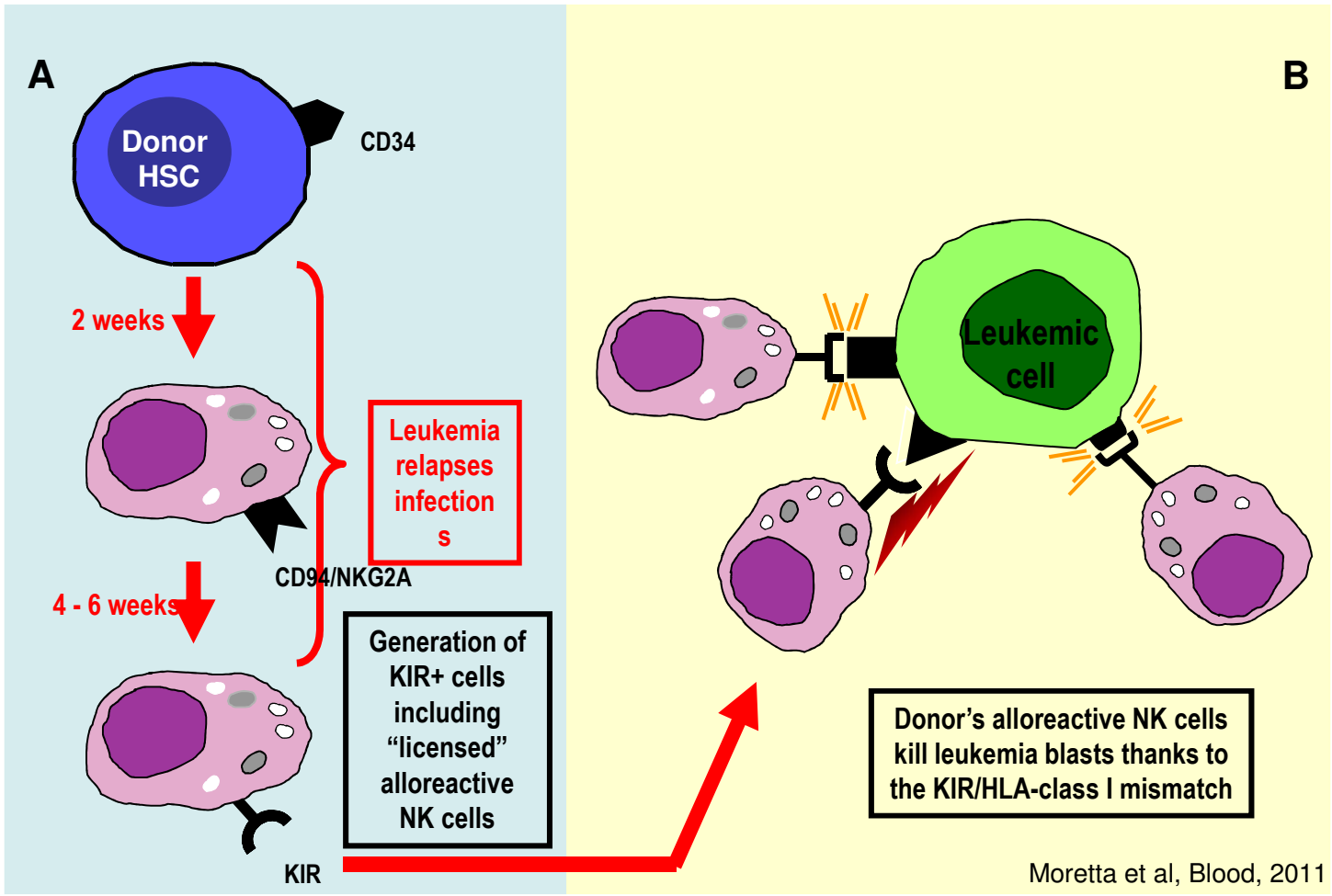
KIR specific for patient's HLA-class I alleles + NKG2A

ALL and AML:
Leukemia-free survival by NK alloreactivity



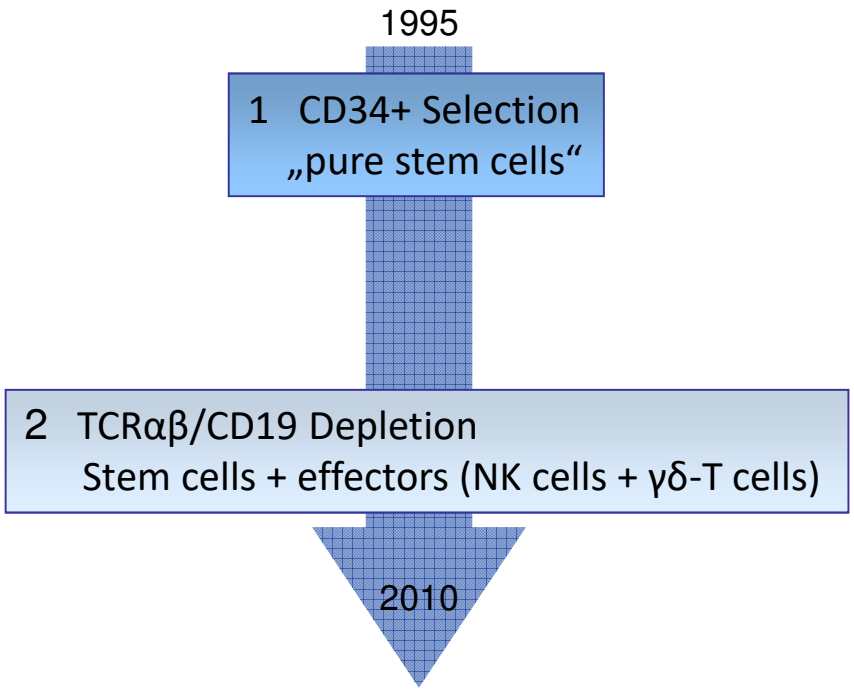
Updated June 2010

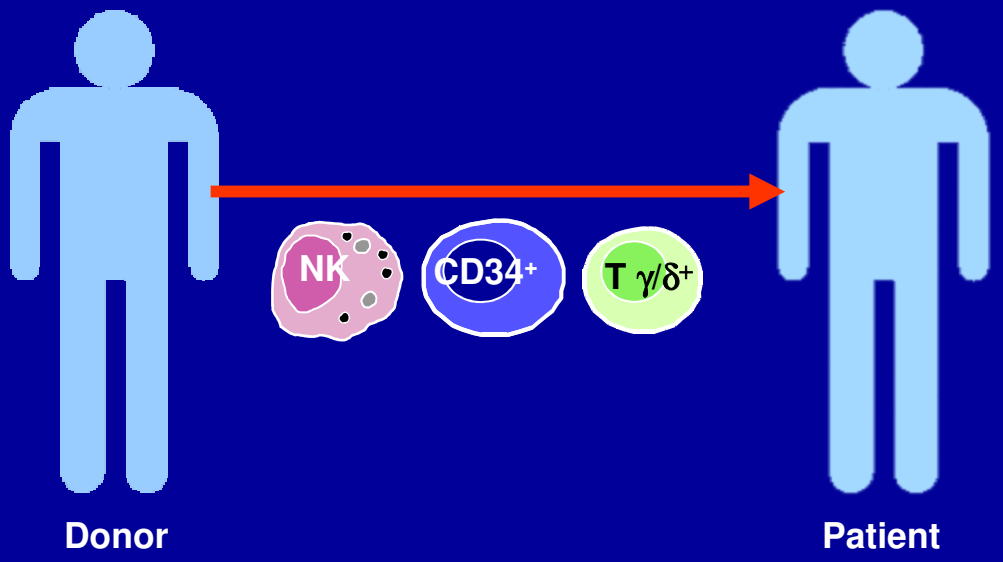
Alloreactive NK cells in haploidentical HSCT



Moretta et al, Blood, 2011

Haploidentical donors:
evolution of T-cell depletion strategy

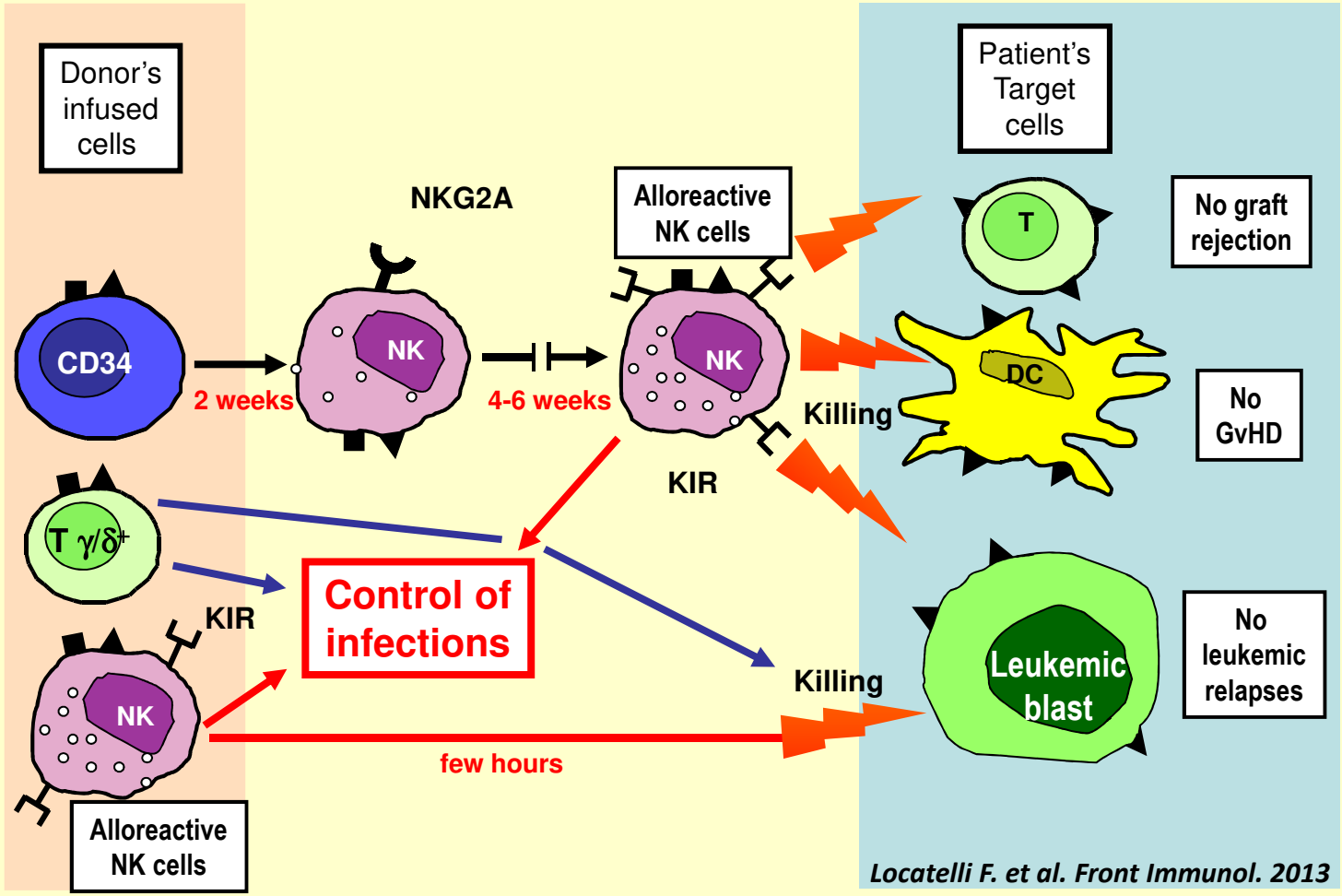




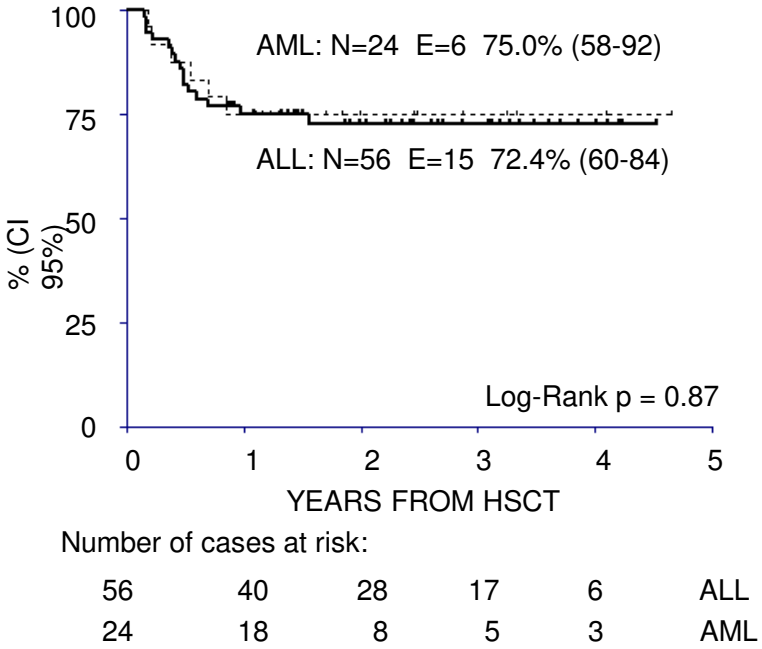
Infusion of TCRγ/β-depleted HSC + effector cells

Coll. F. Locatelli, IRCCS Bambino Gesù

A novel strategy for HSC transplantation from haploidentical donors



Leukemia Free Survival by disease



Dept of Exp Med, University of Genova
Alessandro Moretta
Simona Sivori
Roberta Castriconi
Emanuela Marcenaro
Mariella Della Chiesa

IST, Genova
Maria Cristina Mingari
Daniela Pende
Massimo Vitale
Gabriella Pietra

G. Gaslini Institute, Genova
Cristina Bottino
Claudia Cantoni
Michela Falco
Grazia Maria Spaggiari
Stefania Marcenaro
Francesco Frassoni

S. Matteo Hospital University of Pavia, Pavia and Bambino Gesù Hospital, Roma
Franco Locatelli
Rita Maccario
Daniela Montagna
Maria Ester Bernardo
Alice Bertaina

S. Martino Hospital, Genova
Andrea Bacigalupo

Bambino Gesù
OSPEDALE PEDIATRICO