6th World Congress on
Cell & Stem Cell Research
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Identify the melocular mechamisms that regulate defective NK cell development in aged mice

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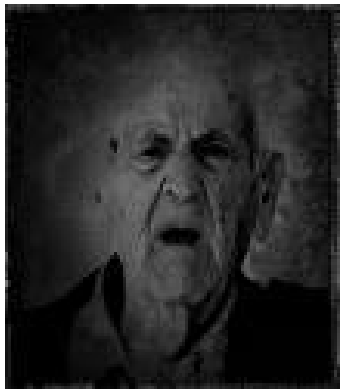
Physiologic aging



Baby



Adult



Aged

Decreased efficacy to vaccination

More vulnerable to tumor

More susceptible to infectious diseases:
H5N1, West Nile virus (WNV), severe acute respiratory syndrome (SARS)

NK cells and Immunosenescence?

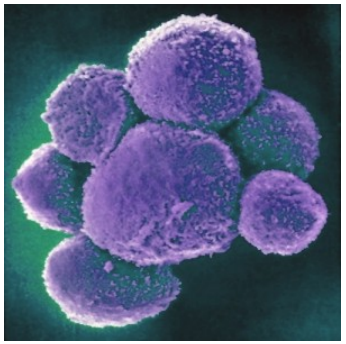
Innate and adaptive immunity?

Table 1. Key aspects of mouse T-cell aging.

$CD4^+$ T cells	$CD8^+$ T cells
Reduced T-cell receptor signaling intensity	Decline in responsiveness to newly encountered antigens
Defects in activation, differentiation and expansion after stimulation	Age-related declines in $CD8^+$ T-cell repertoire diversity
Reduced production of interleukin-2	Nonmalignant expansion of individual $CD8^+$ T-cell clones
Impaired ability to provide cognate help to B cells after immunization	Impaired generation of $CD8^+$ T-cell memory

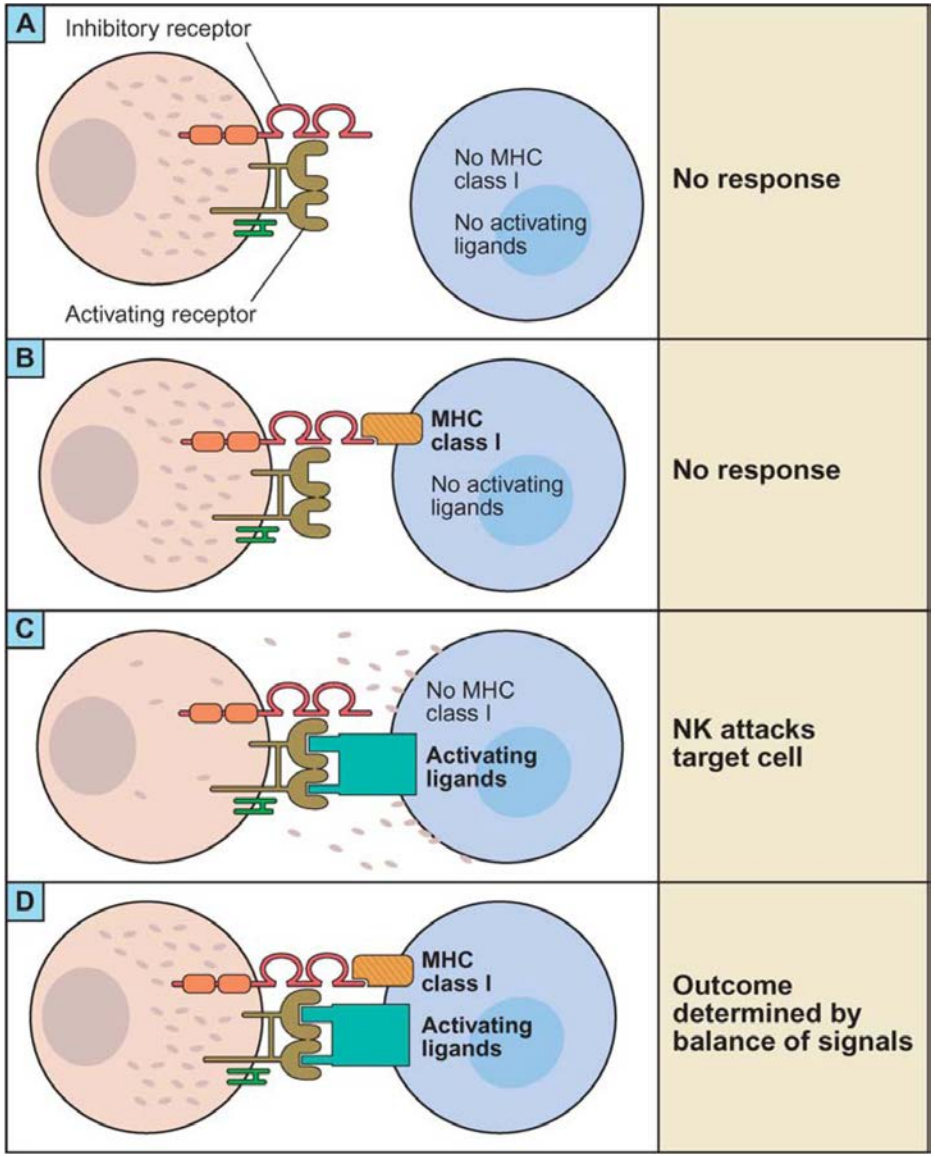
Maue A, et al. *Trends in Immunology, 2009*

Natural killer (NK) cells



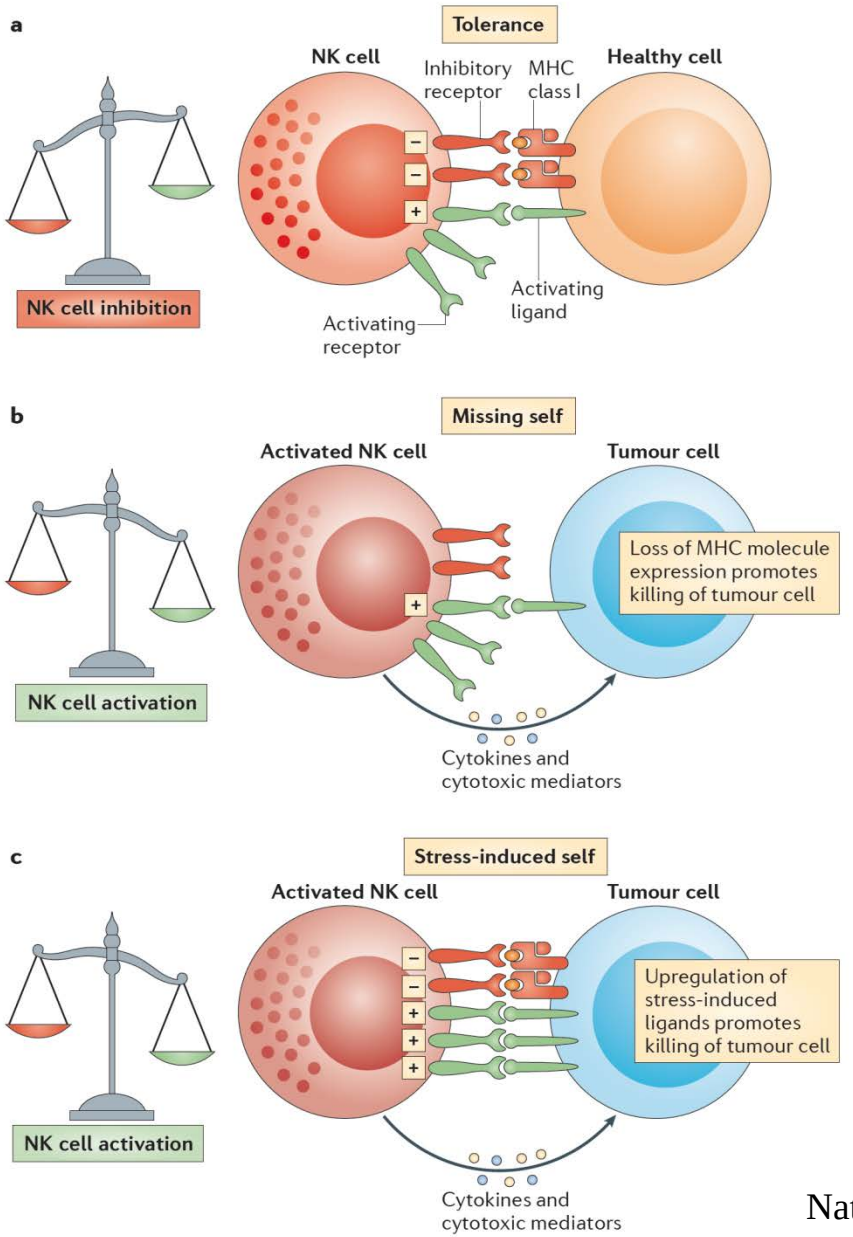
- Cytolytic lymphocytes
- Derived from bone marrow
- Innate immune system: NK cell receptors are encoded in the germline and do not undergo somatic recombination like B and T cell receptors
- NK cells are a key component of the innate immune system, providing early cellular defense against viruses and intracellular pathogens, and contributing to the early detection and destruction of transformed cells

NK cell responses to targets: “Missing-self” revisited



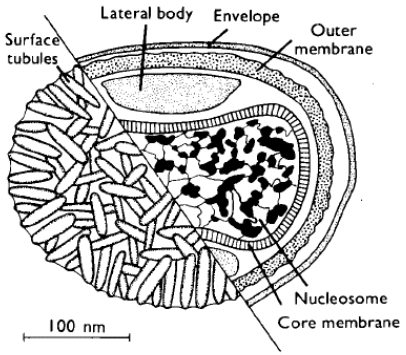
Lewis L. Lanier *Ann. Rev. Immunol* 2005

The rheostat concept of NK cell responsiveness



Nature reviews/Immunology, 2012

Orthopoxvirus (OPV)



- DNA viruses, ≈200 Kb, ≈200 proteins
- The genome among all OPV are highly conserved (90% overall) → strong antigenic cross reactivity
- Variola virus, humans → smallpox
- Ectromelia virus (ECTV), laboratory mouse → mousepox
- Vaccinia virus (VACV). Poorly or non pathogenic in humans and mice → Vaccine against both, smallpox and mousepox
- Cowpox virus → First vaccine

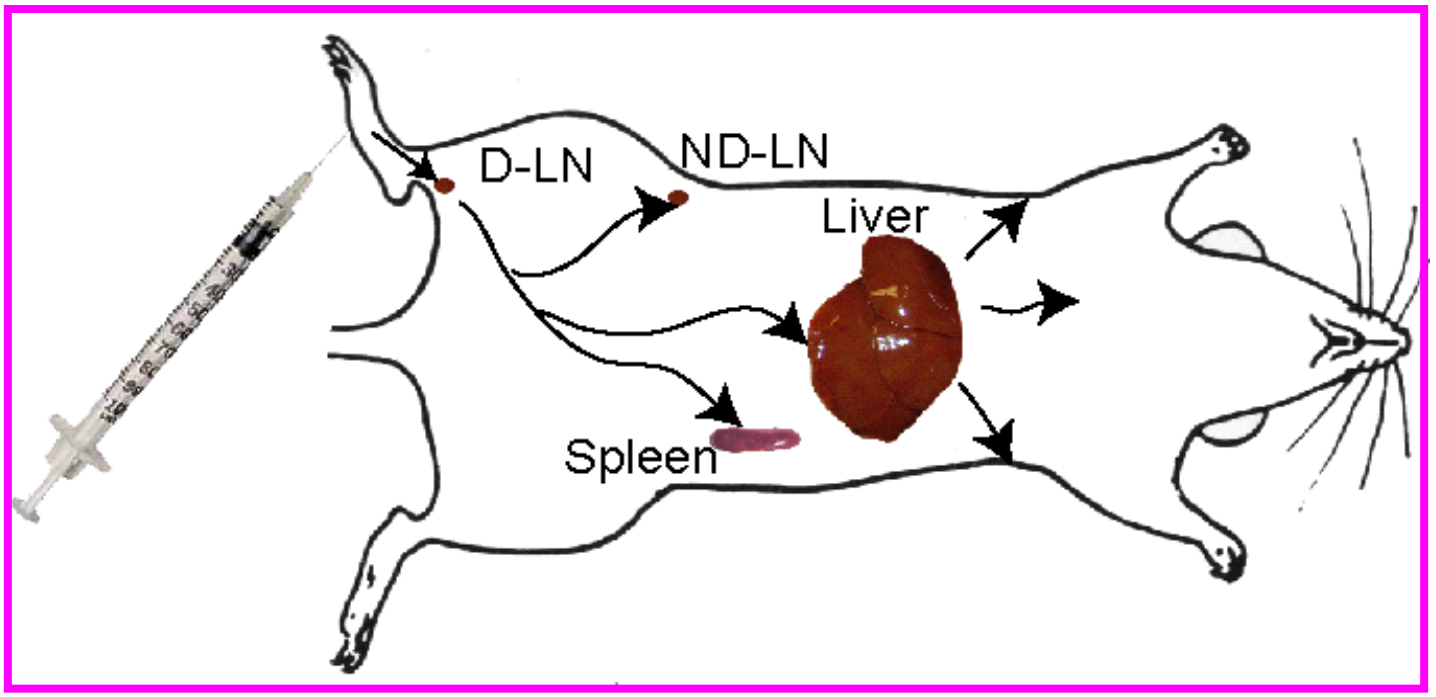
Advantages of the ECTV model

- ECTV is a mouse pathogen
- Mousepox is very similar to smallpox
- Mousepox can be prevented by immunization with VACV

- *Resistant mouse strains*
  C57BL/6 (B6), 129
  Mechanism of natural resistance:
  Role of T cells, Abs, NK cells, aging etc.

- *Susceptible mouse strains*
  BALB/C, DBA/2J
  Mechanisms of acquired resistance
  Role of Immune Response Modifiers in virulence

Measurement of virus titers and cellular responses



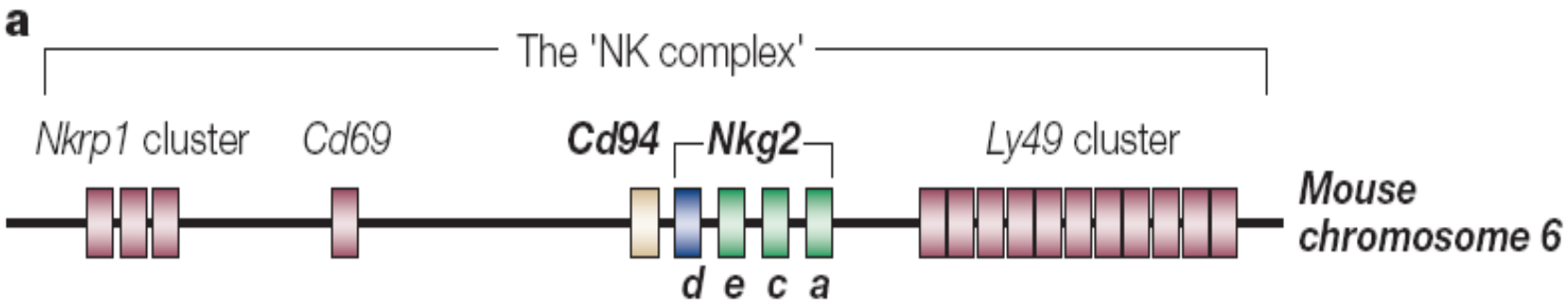
7 dpi	B6	BALB/C
Footpad, PFU	10^8	10^8
Spleen, PFU	10^4	10^8
Liver PFU/gram of liver	10^5	10^9

ML Delano and DG Brownstein. *J. Virol*., 1995.

Innate resistance to lethal mousepox is genetically linked to the NK gene complex on chromosome 6 and correlates with early restriction of virus replication by cells with an NK phenotype

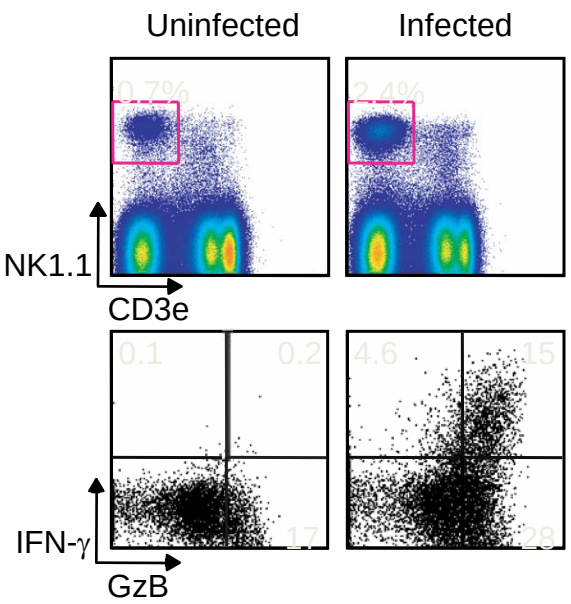
B6 × DBA/2J

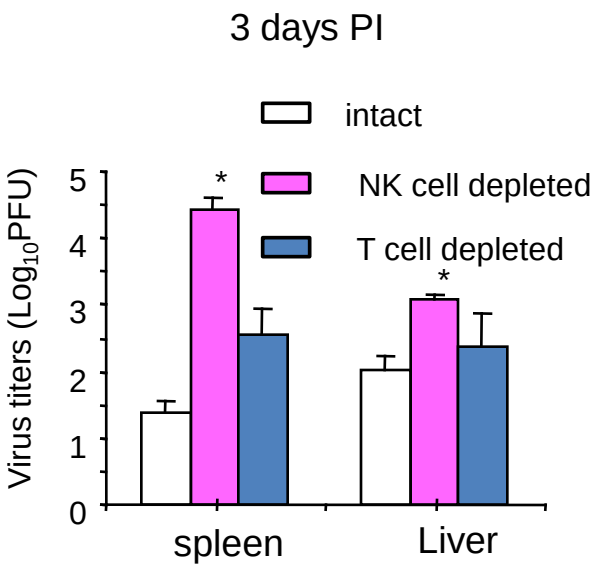
A gene responsible for the resistance of B6 mice to mousepox (Rmp1) maps to the NKC region of mouse chromosome 6



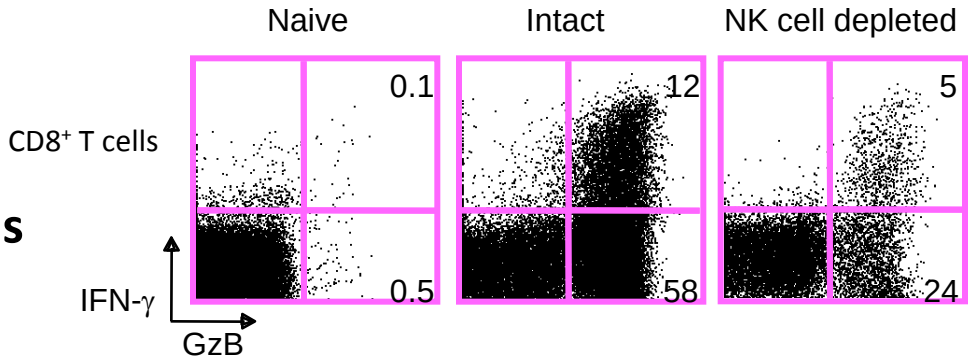
David H. Raulet *NATURE REVIEWS* | *IMMUNOLOGY 2003*

What is the role of NK cell responses in protection (direct vs. indirect) to ECTV infection?



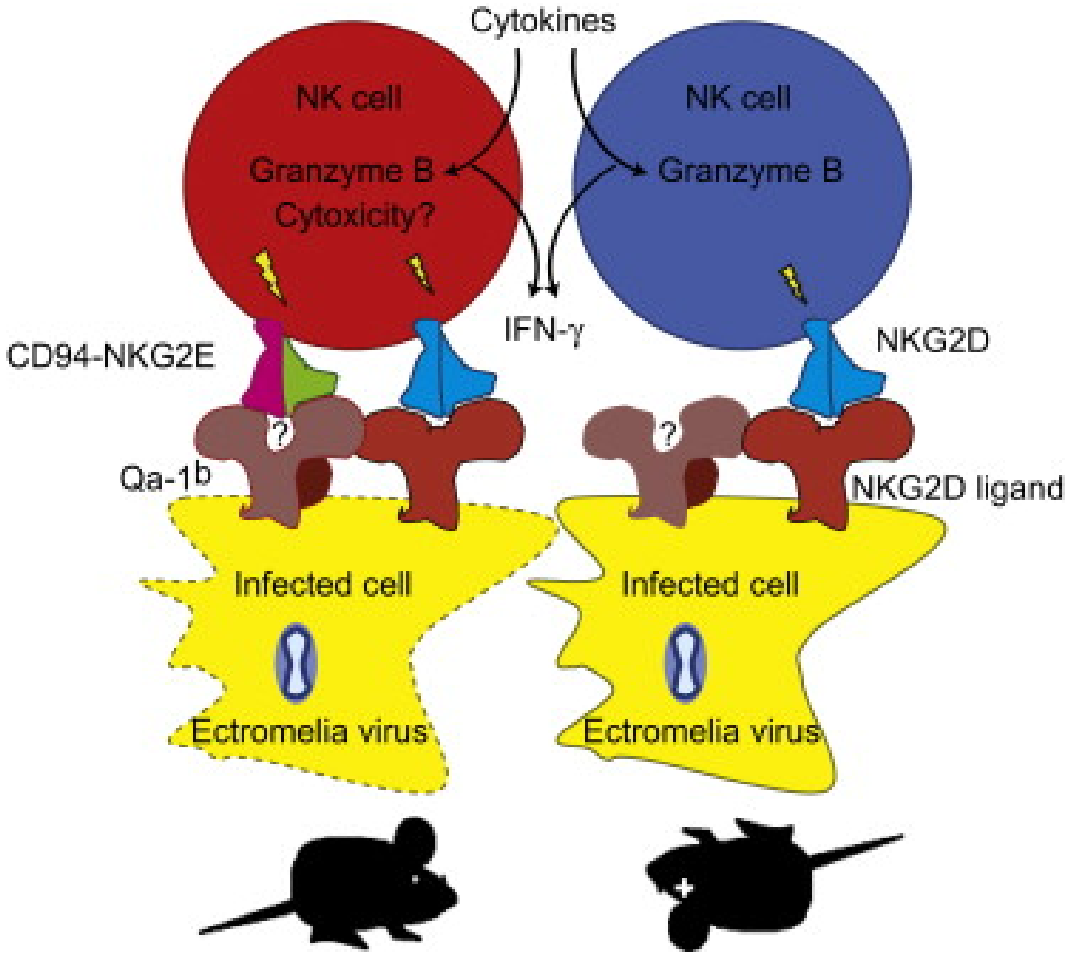


CD8⁺ T cells



Plos Pathogens, 2008

What are the activating receptors involved in the NK cell responses to ECTV infection ?



CD94-NKG2E

↓

Qa-1^{b}-peptide?

NKG2D: costimulator

Immunity, 2011

C57BL/6 (B6) mice are naturally resistant to mousepox

- Resistance to mousepox needs both innate and adaptive immune responses
- Antibodies and $CD8^+$ T Cells Are Complementary and Essential for Natural Resistance to mousepox
- NK cells are required for the resistance to mousepox

Published September 27, 2010

JEM

Article

Age-dependent susceptibility to a viral disease due to decreased natural killer cell numbers and trafficking

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Immune Cell Development and Host Defense Program, Fox Chase Cancer Center, Philadelphia, PA 19111

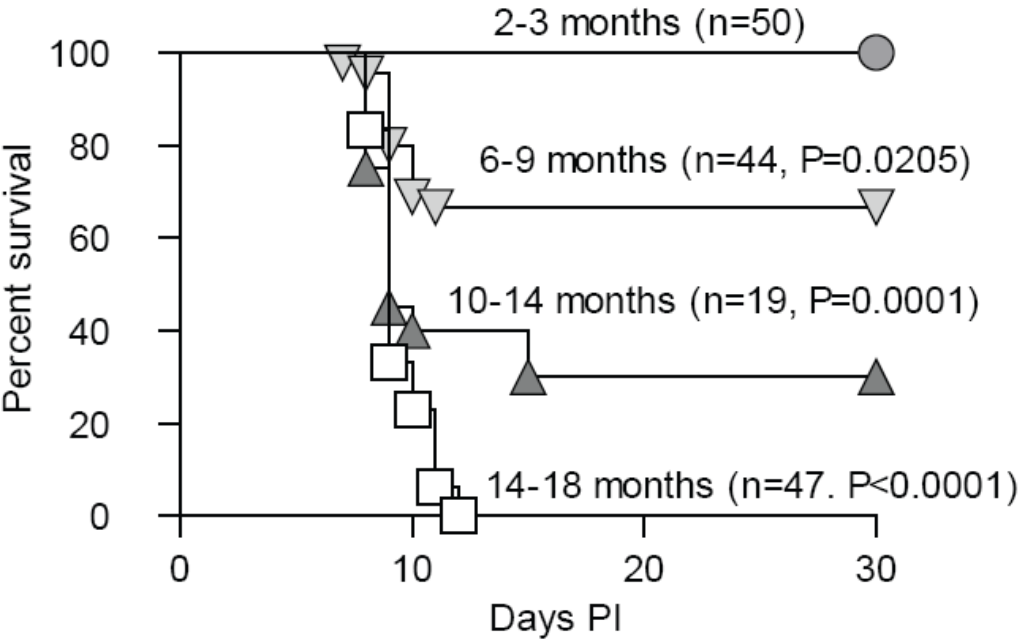
"Faculty of 1000"

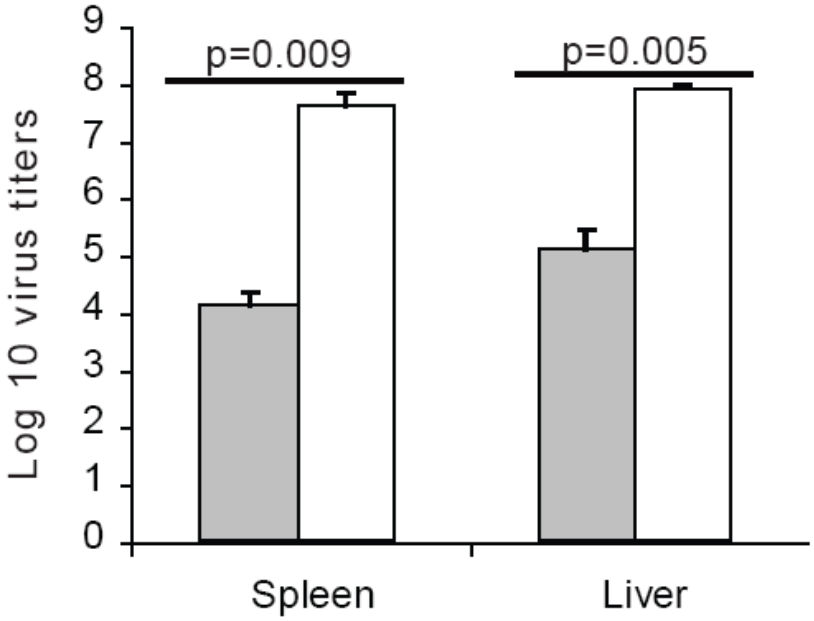
FFa 11

It demonstrated an important role for natural killer (NK) cells in resistance to viral infections in aged mice, which has implications for susceptibility to viral infections in aging humans as well as in children who have a defect in NK cell number, maturity or function.

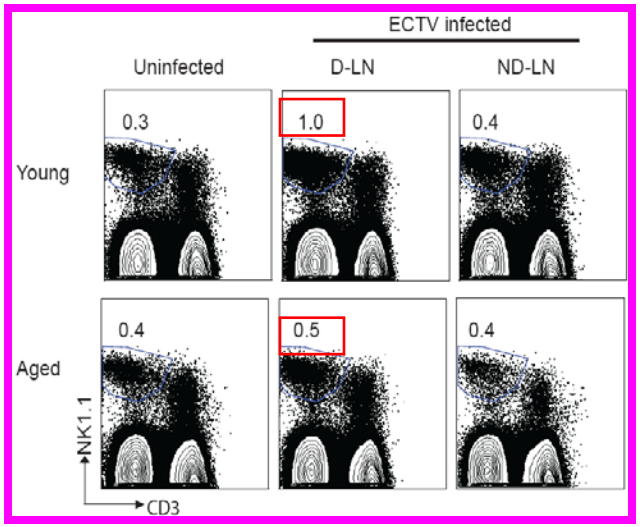
Evaluated by *Ramsay Fuleihan*

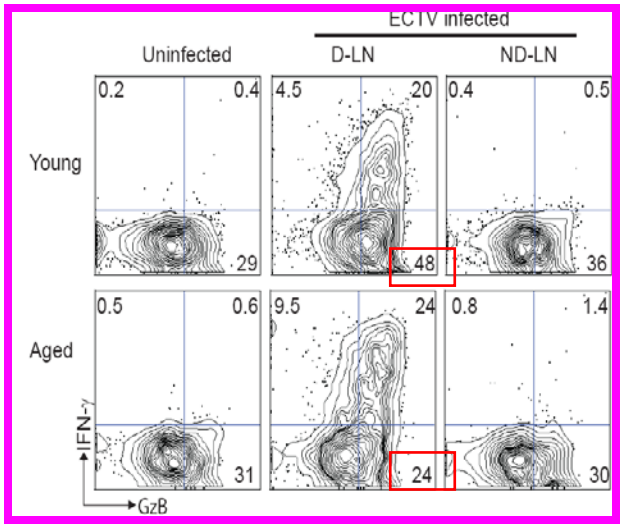
The natural resistance in B6 mice to mousepox declines as they age

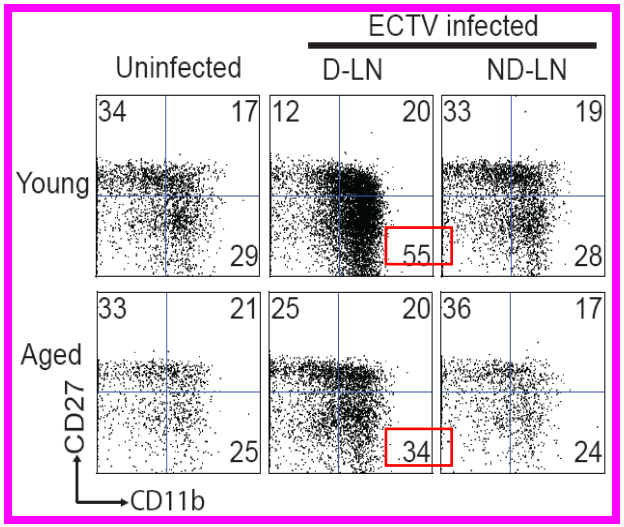


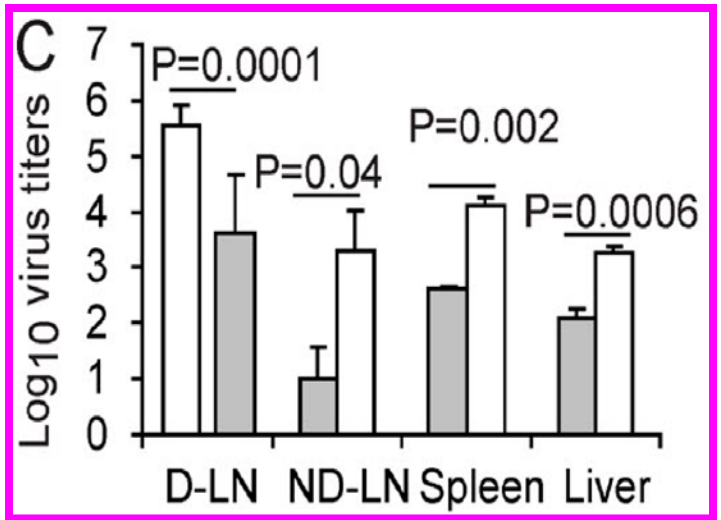


Defective NK cell responses in aged mice result in increased early virus loads in organs

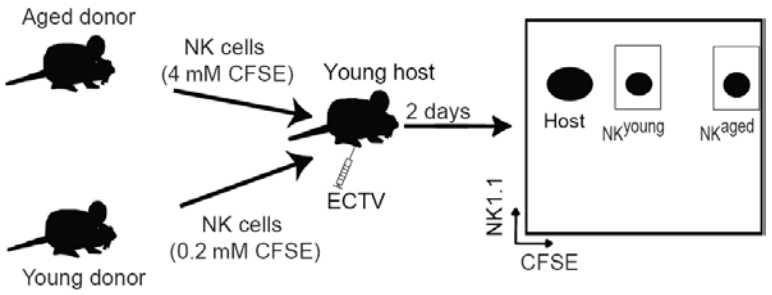


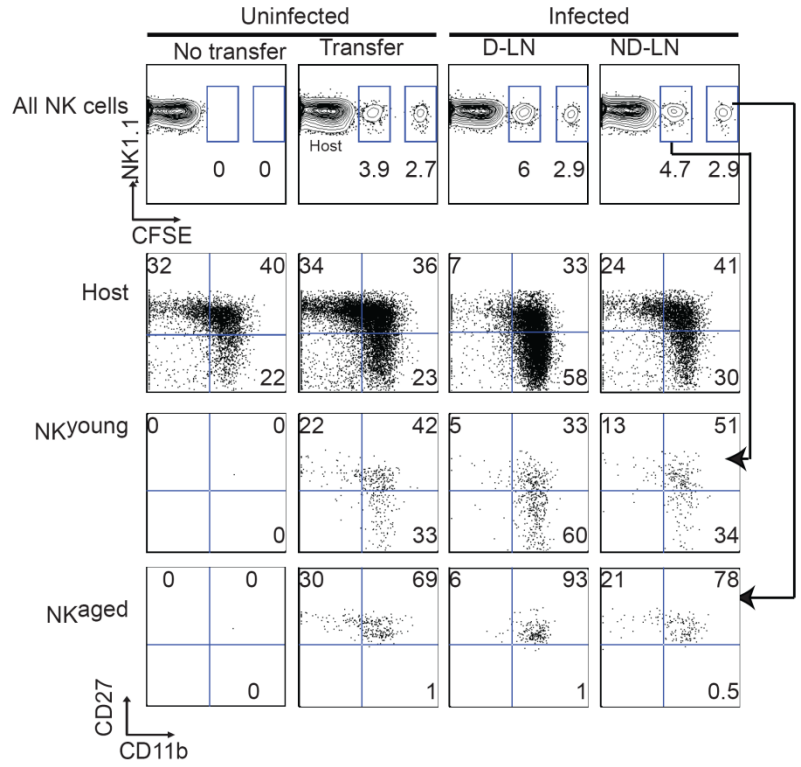


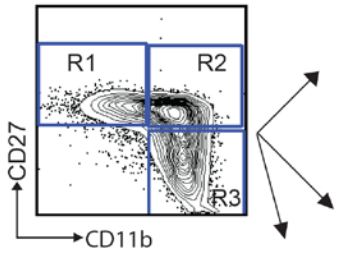


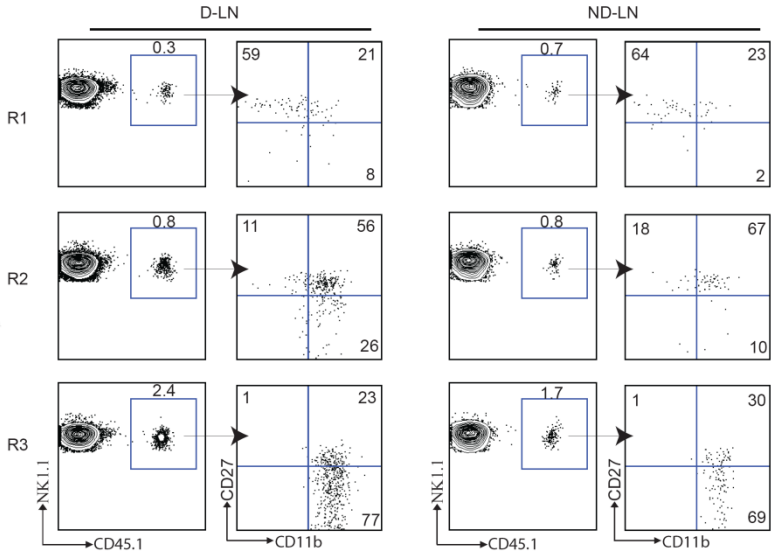


The mature NK cells of aged mice have intrinsic trafficking defects

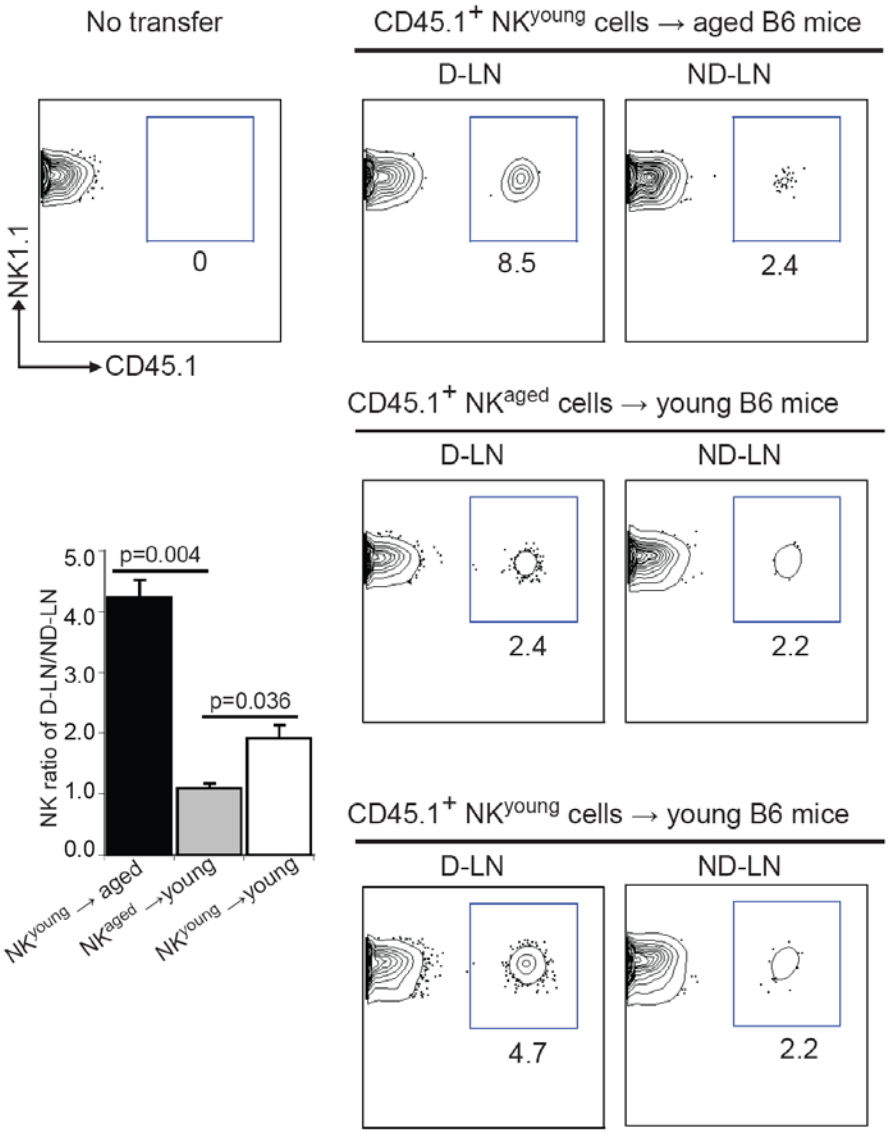


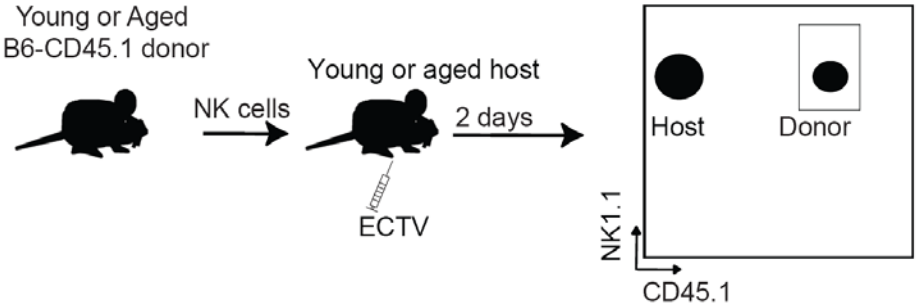


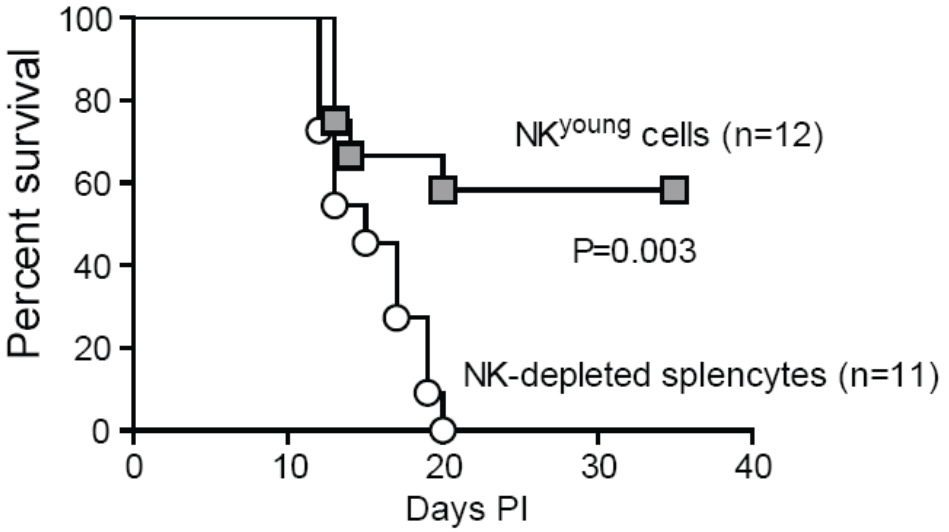




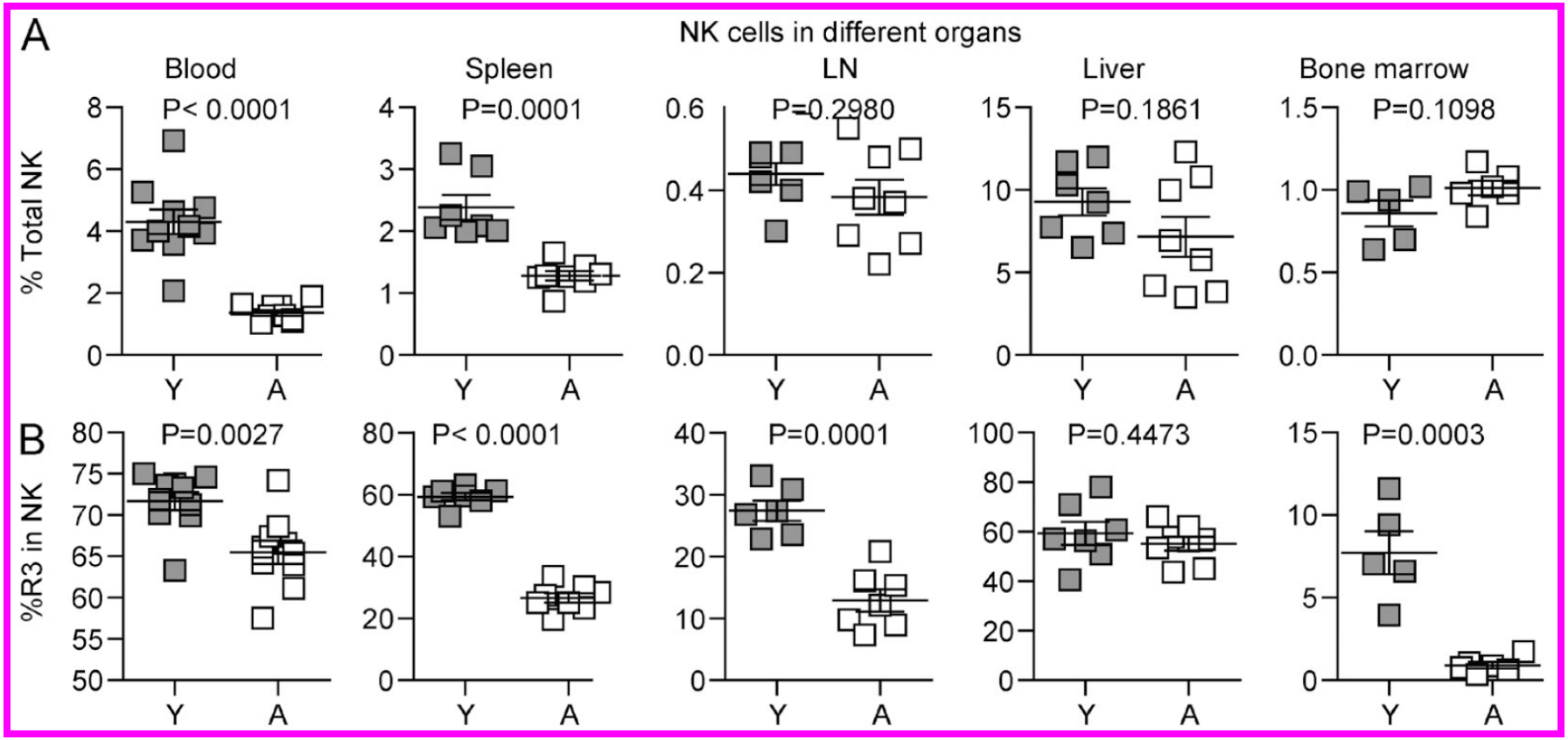
NK cells from young mice migrate to the D-LN of aged mice and protect them from mousepox





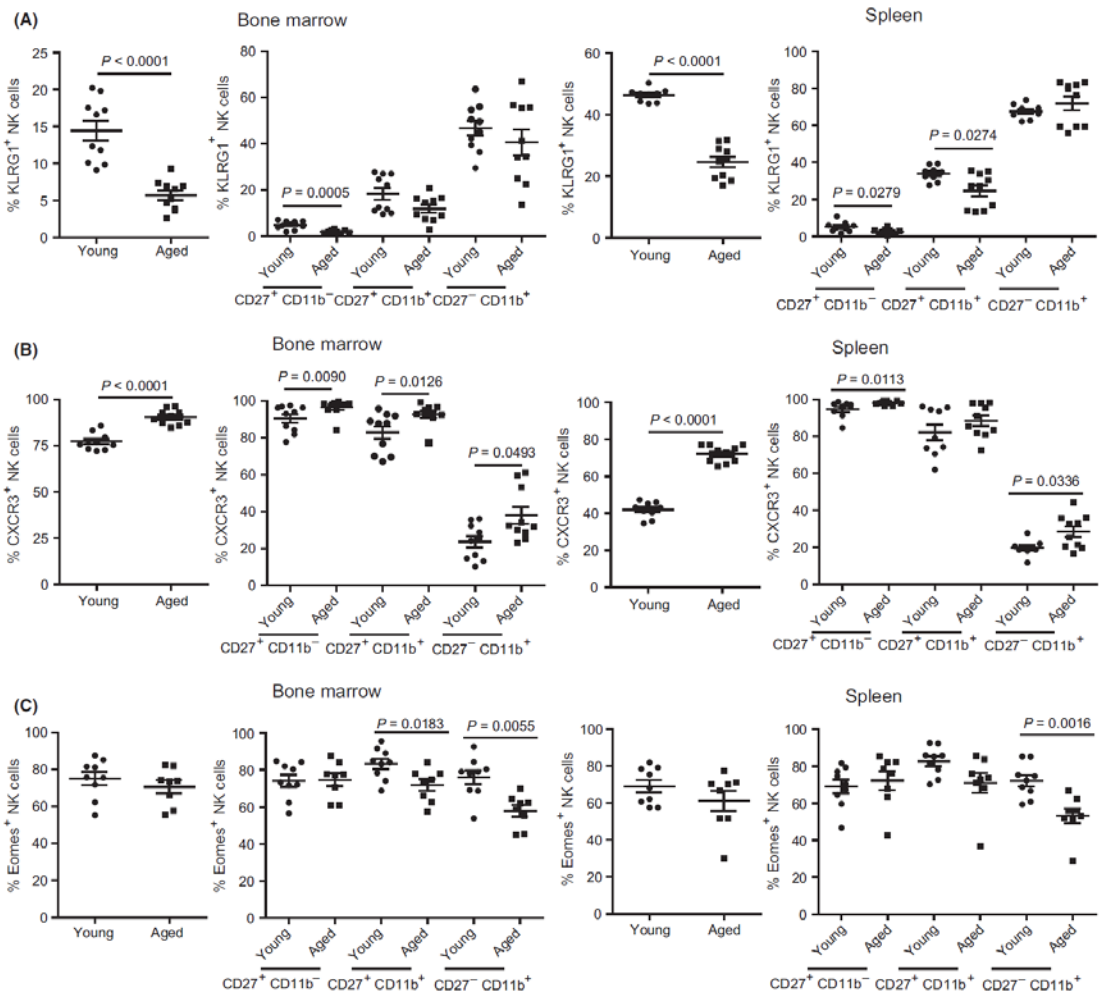


Decreased total and mature NK cells in various organs of aged mice



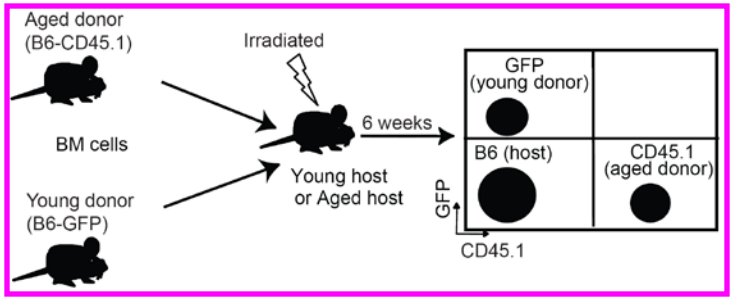
The mechanisms for the defective NK cell development in the aged mice?

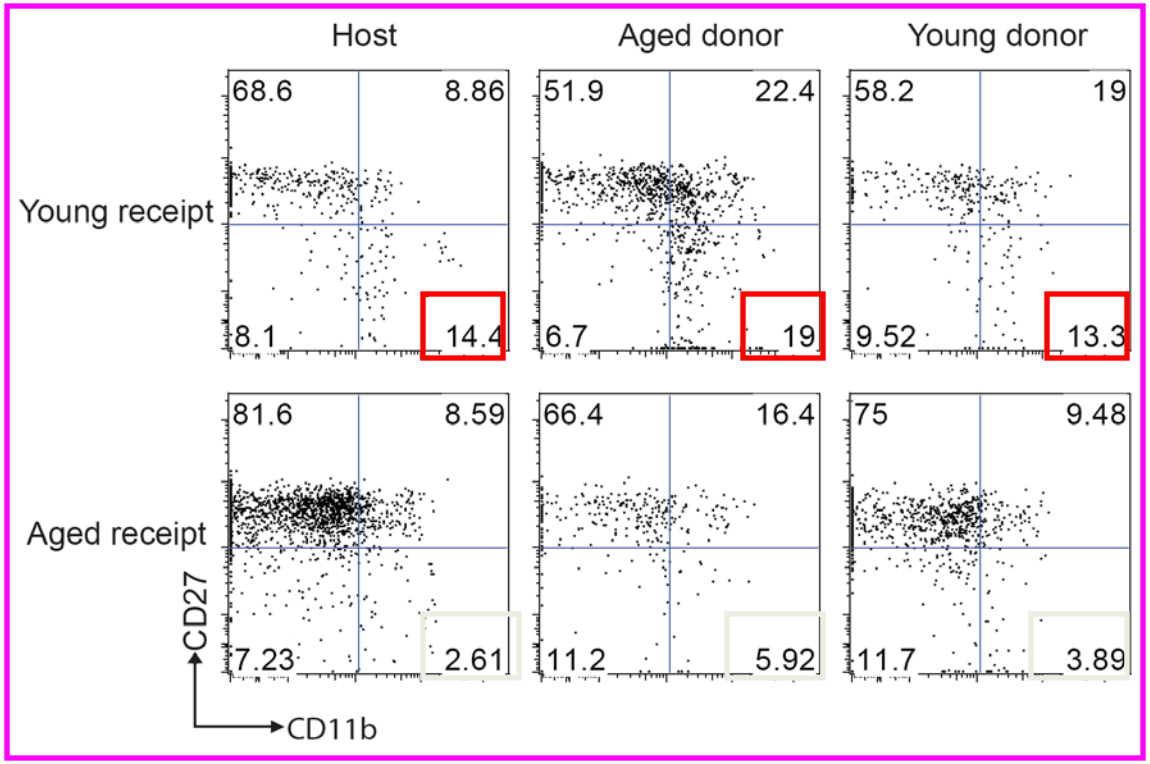
NK cells in aged mice have an immature phenotype

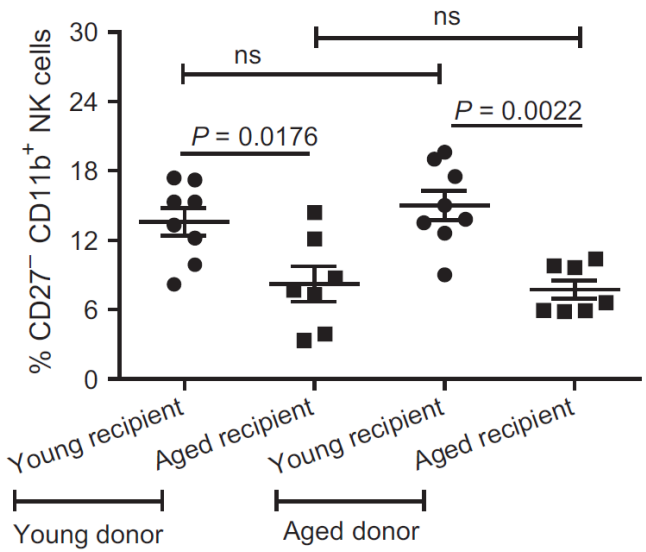


Aging Cell, 2014

Reduced mature NK cells in the aged BM is due to the BM micro-environments

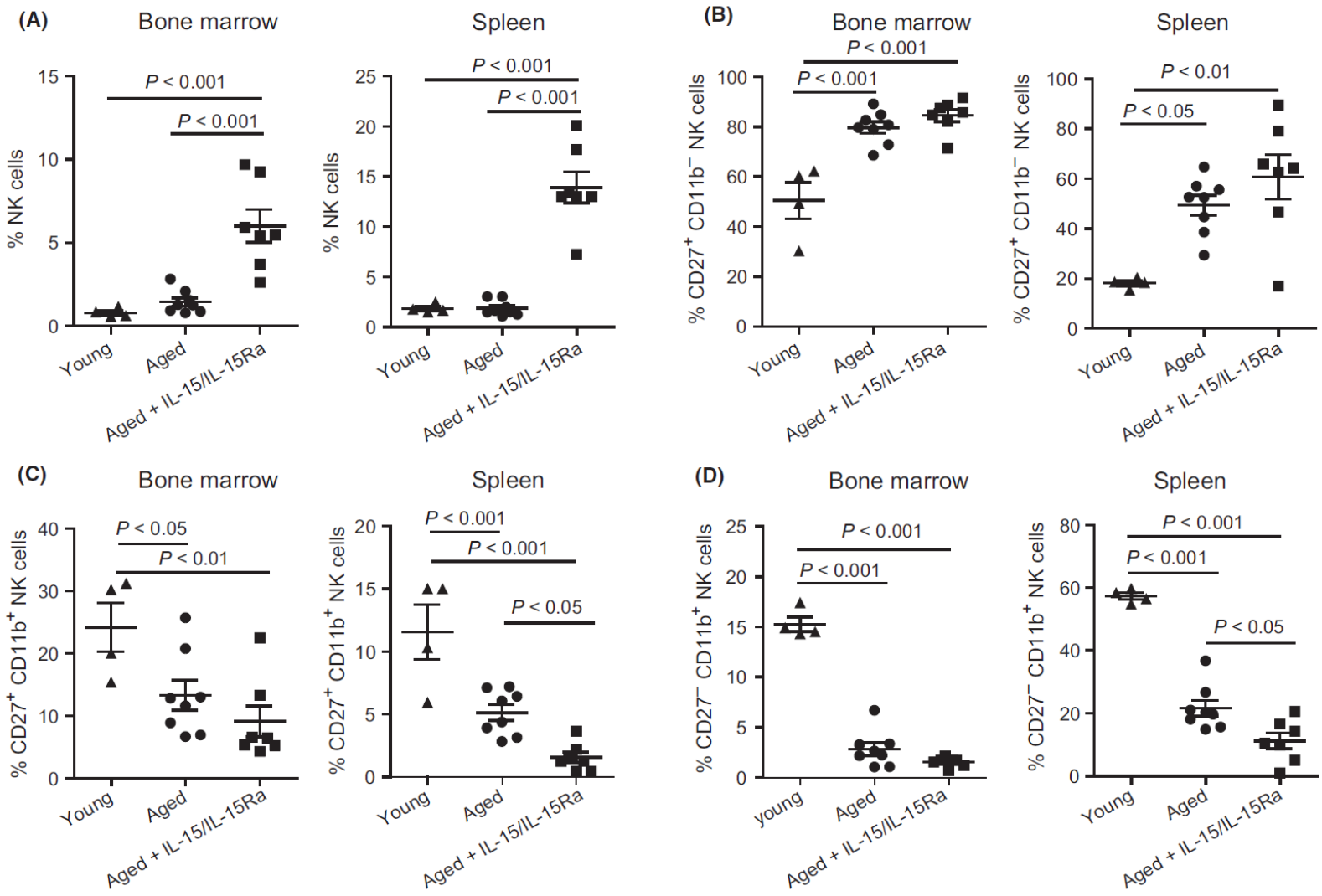






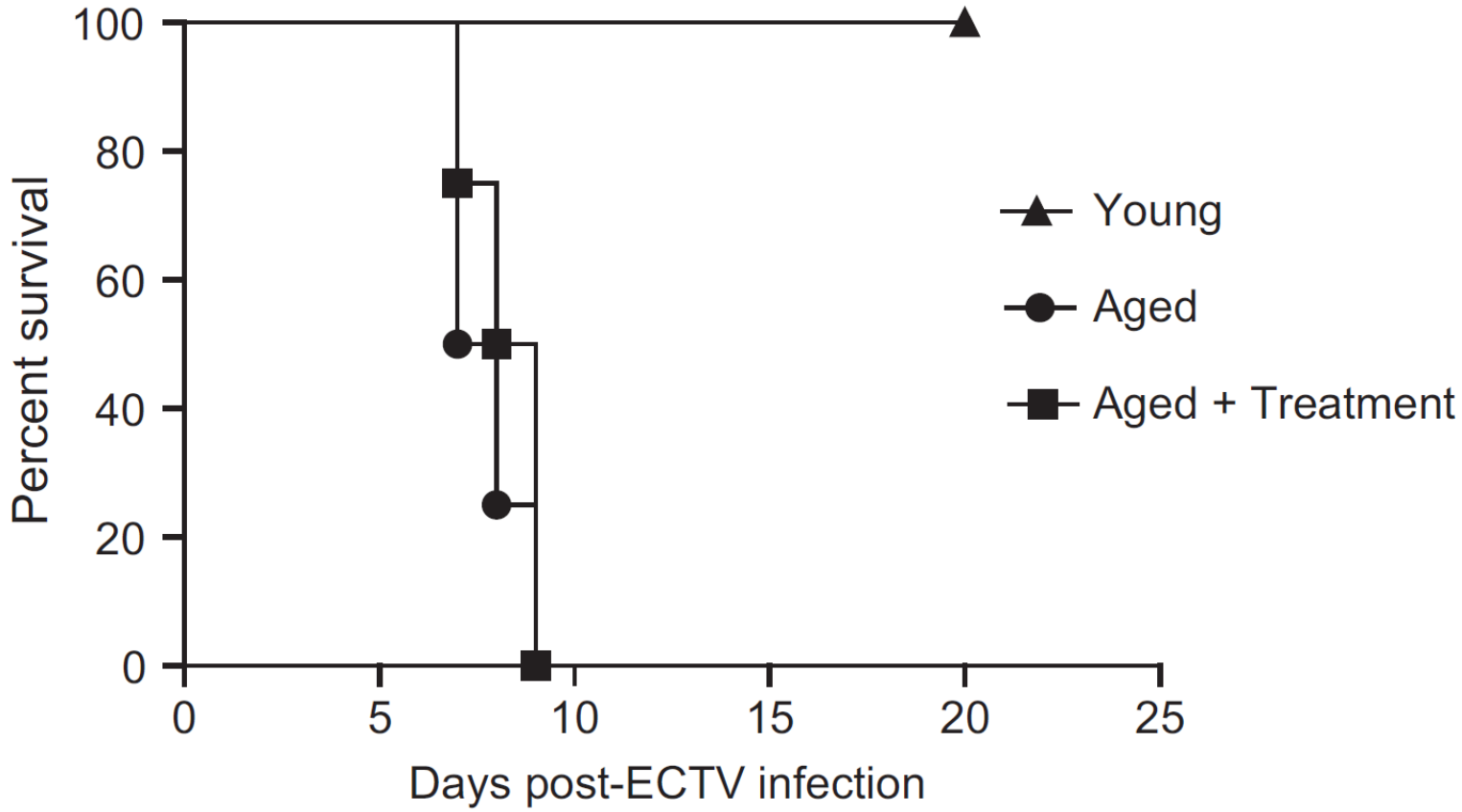
Aging Cell, 2014

Treatment of aged mice with IL-15 and IL-15Ra complex did not increase frequency of mature NK cells



Aging Cell, 2014

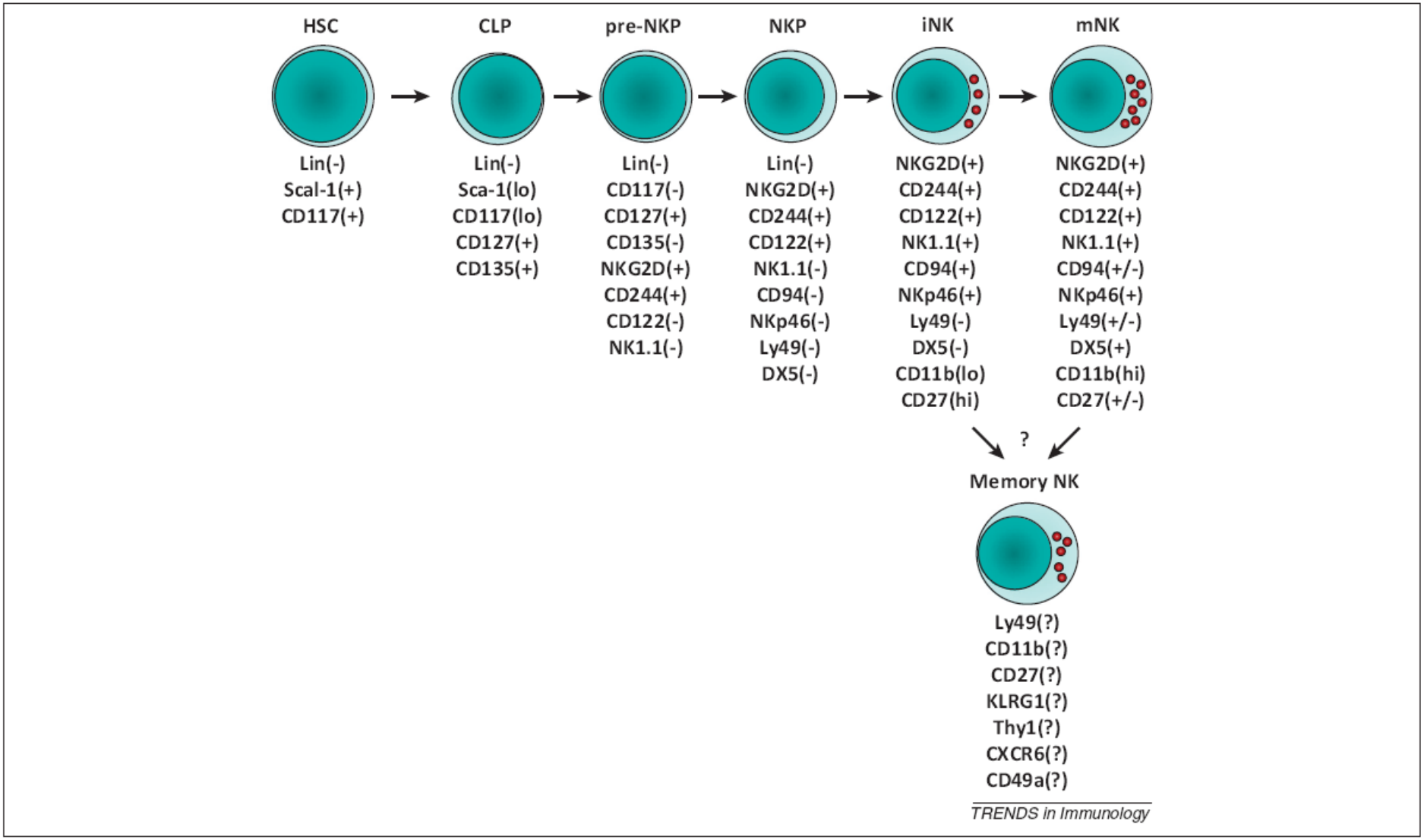
Treatment of aged mice with IL-15 and IL-15Ra complex did not protect aged mice from mousepox



Aging Cell, 2014

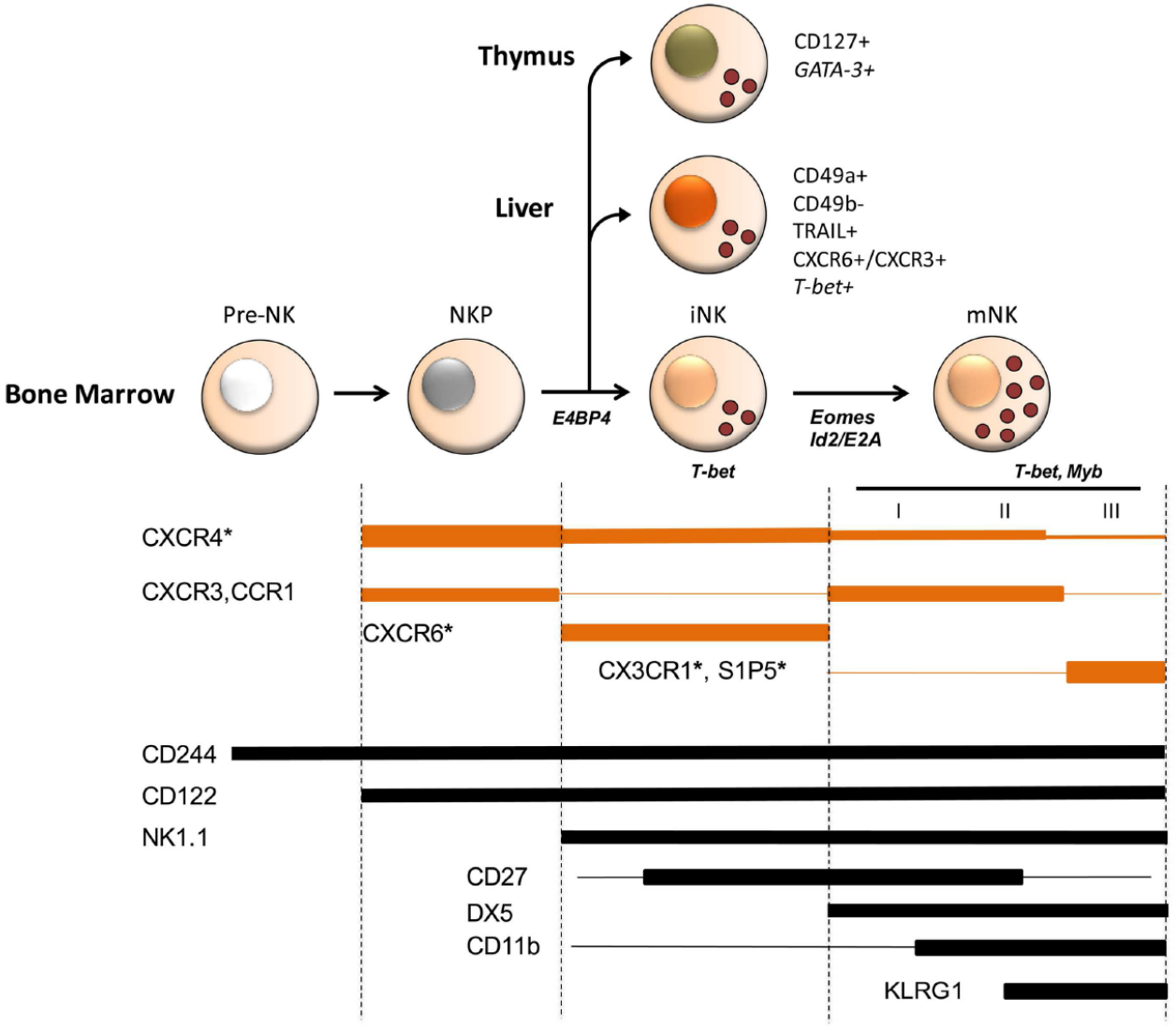
Molecular mechanisms for the defective NK cell development?

Schematic representation of the cellular intermediates of mouse natural killer (NK) cell development



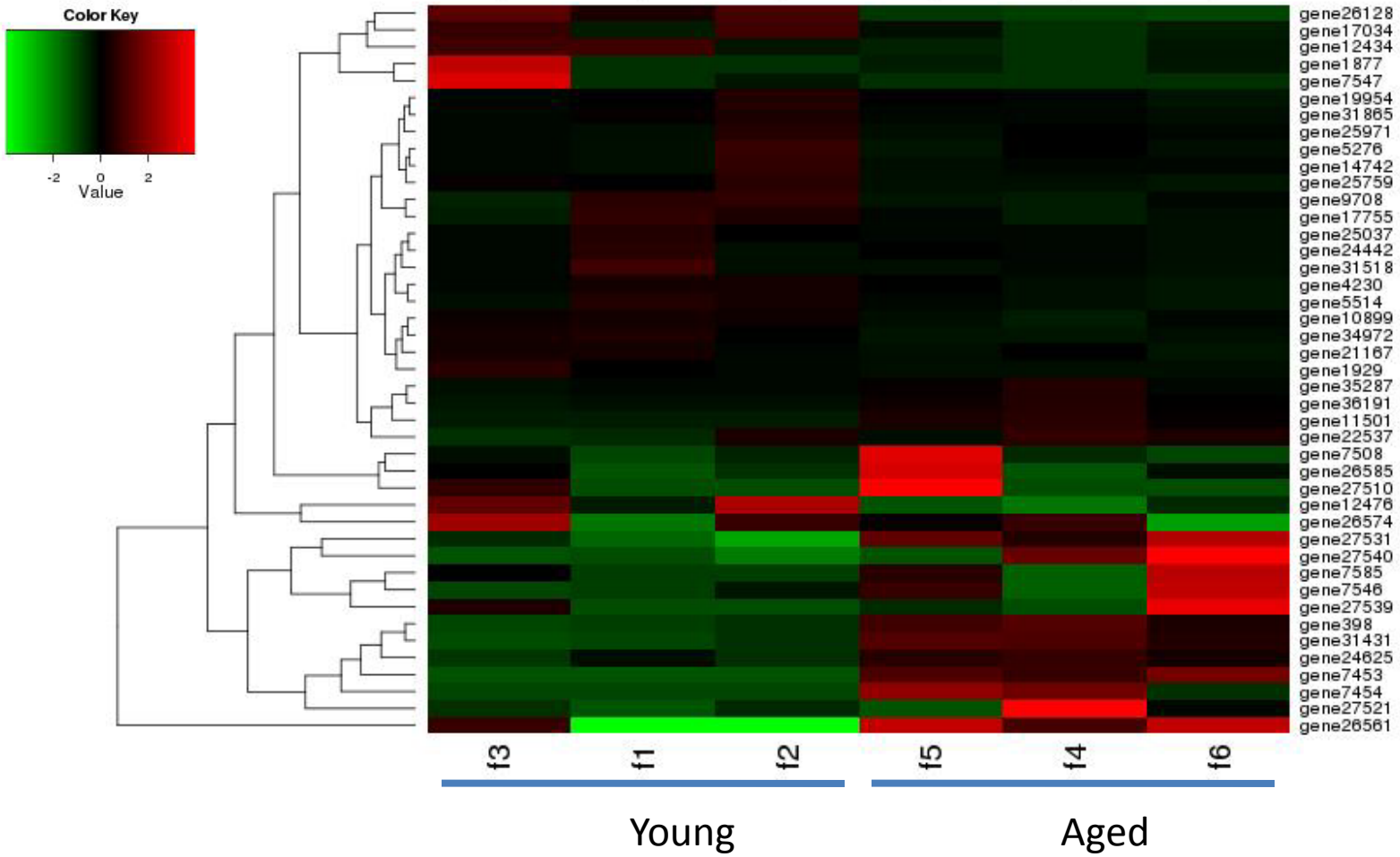
2013

Chemoattractant receptor expression during mouse NK cell development and transcription factors involved in NK cell commitment and maturation



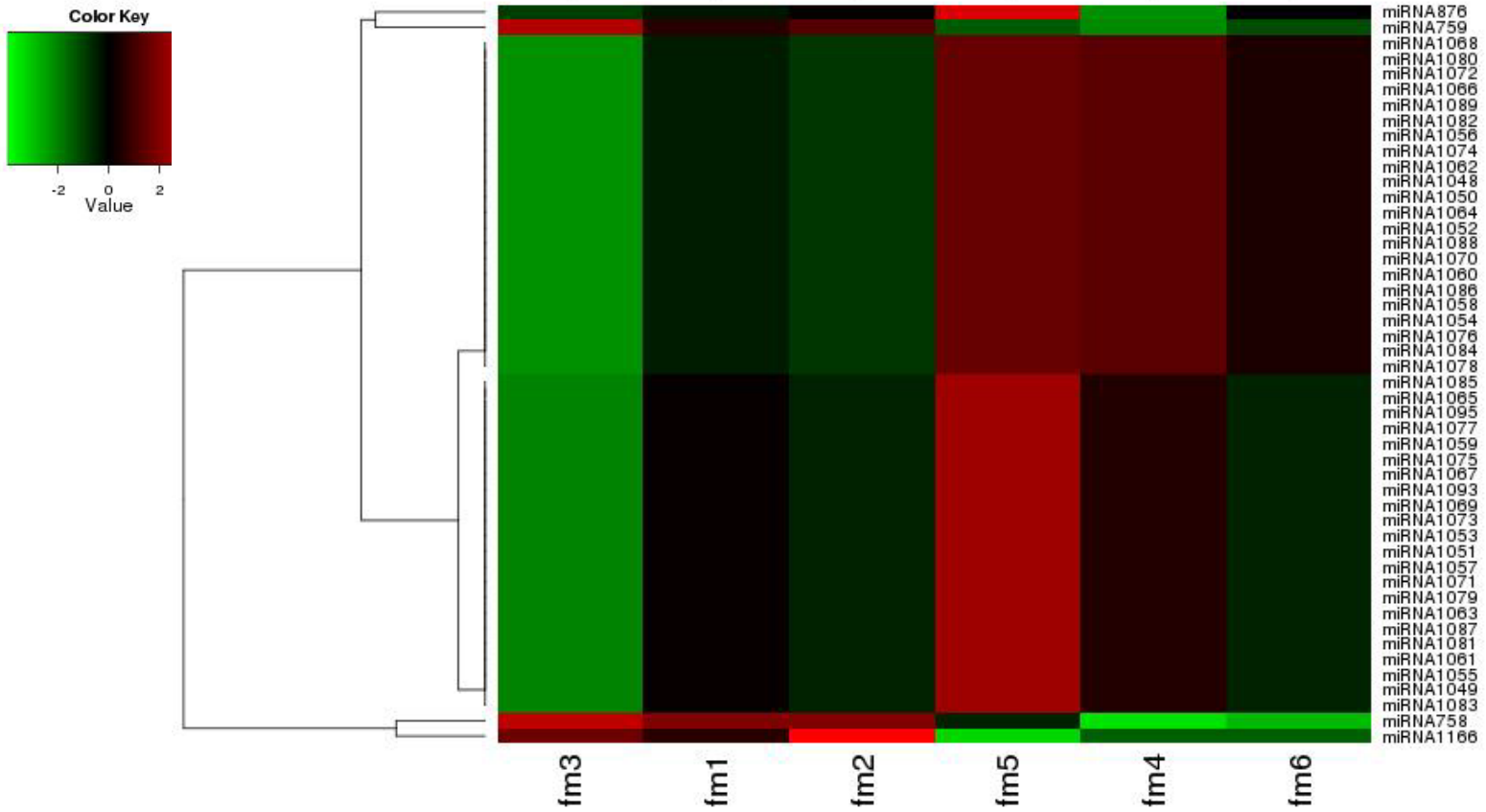
Frontiers in Immunology, 2014

RNseq reveals differential gene expression profiles between young and aged NK cells



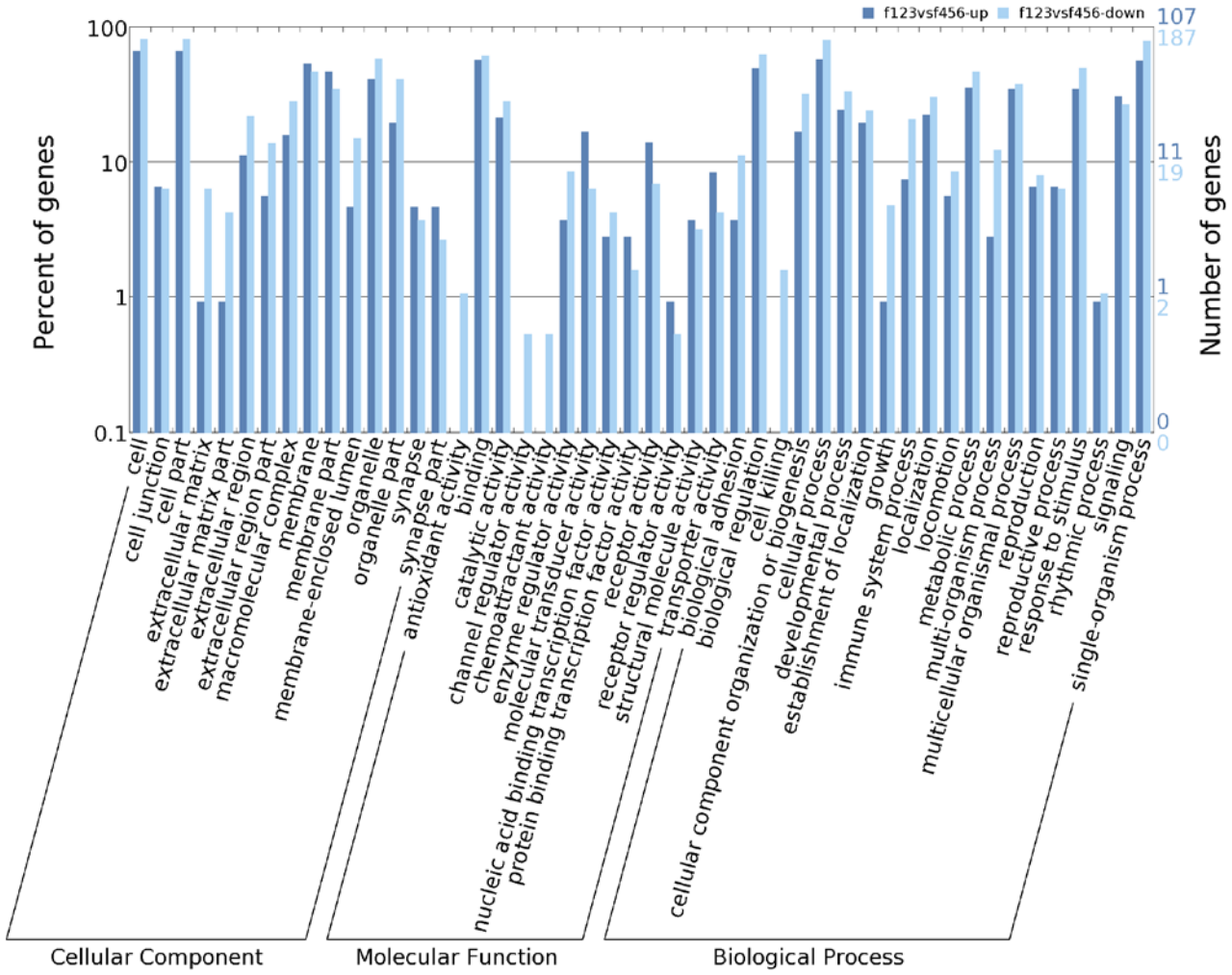
Unpublished data

RNseq reveals differential miRNA expression profiles between young and aged NK cells



Unpublished data

Multiply pathways were differential regulated in young and aged NK cells



Unpublished data

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