
SITC
2017
November 8-12
NATIONAL HARBOR
MARYLAND
Gaylord National Hotel
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Society for Immunotherapy of Cancer

SITC 2017

Innate Lymphocytes

Amir Horowitz, PhD
Assistant Professor of Oncological Sciences
Precision Immunology Institute / Tisch Cancer Center
Icahn School of Medicine at Mount Sinai

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Presenter Disclosure Information

Amir Horowitz, PhD

The following relationships exist related to this presentation:

< No relationships>

Primary role of immune system:

- It protects us from ~1,400 infections with:
  - Viruses
  - Bacteria
  - Fungi
  - Worms
  - parasitic protozoa

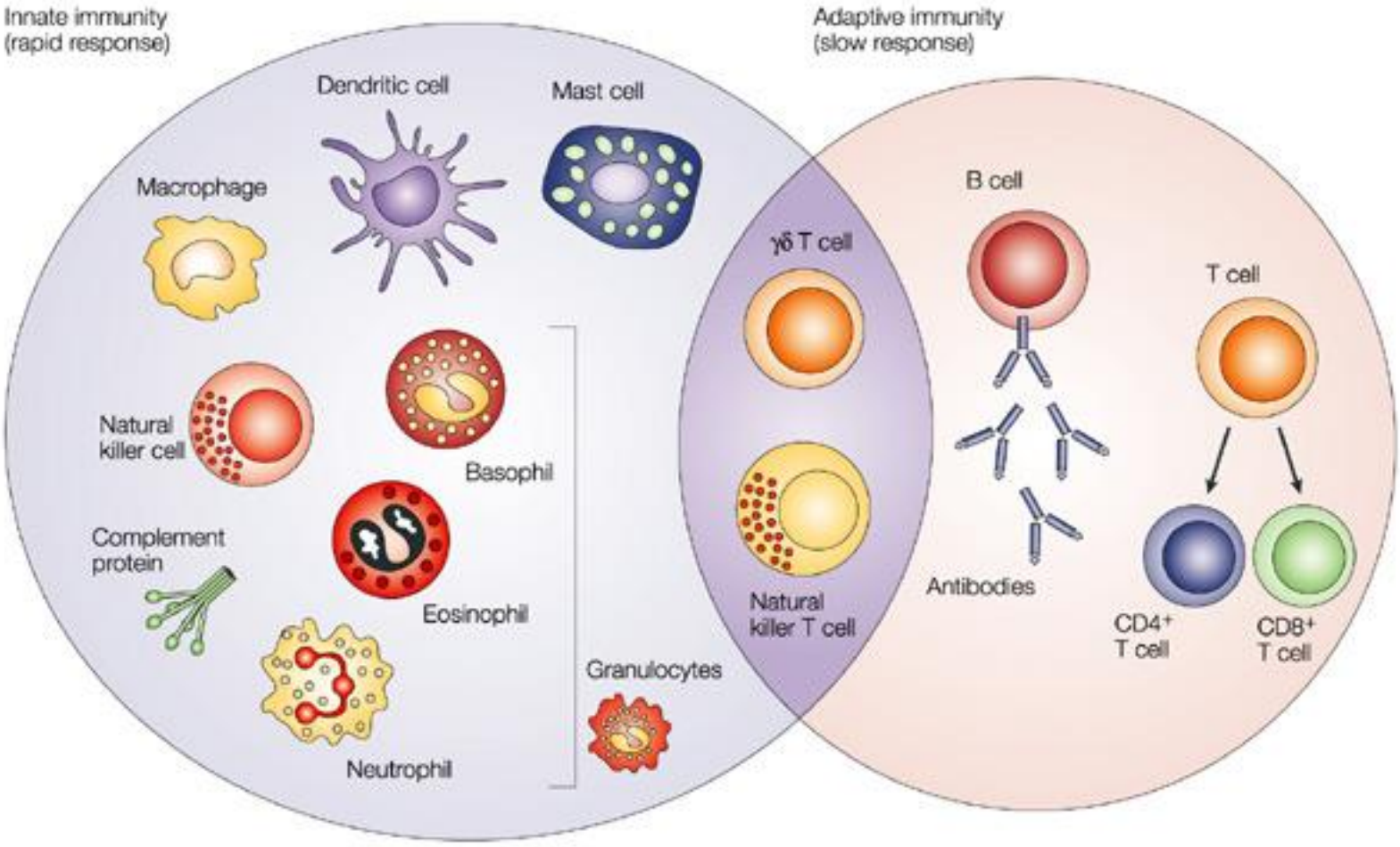
    << 1% total microbial species on planet
- Promotes tissue cleanup, wound repair
- Eliminates abnormal cells including malignant ones
- Also promotes disease when dysregulated (allergies, autoimmunity, transplant rejection, etc.)

Innate Immunity vs. Adaptive immunity

- **Innate immunity** does not require prior sensitization, and little adaptation through life experience
- limited numbers of distinct receptors; recognize highly conserved features of classes of microbes.

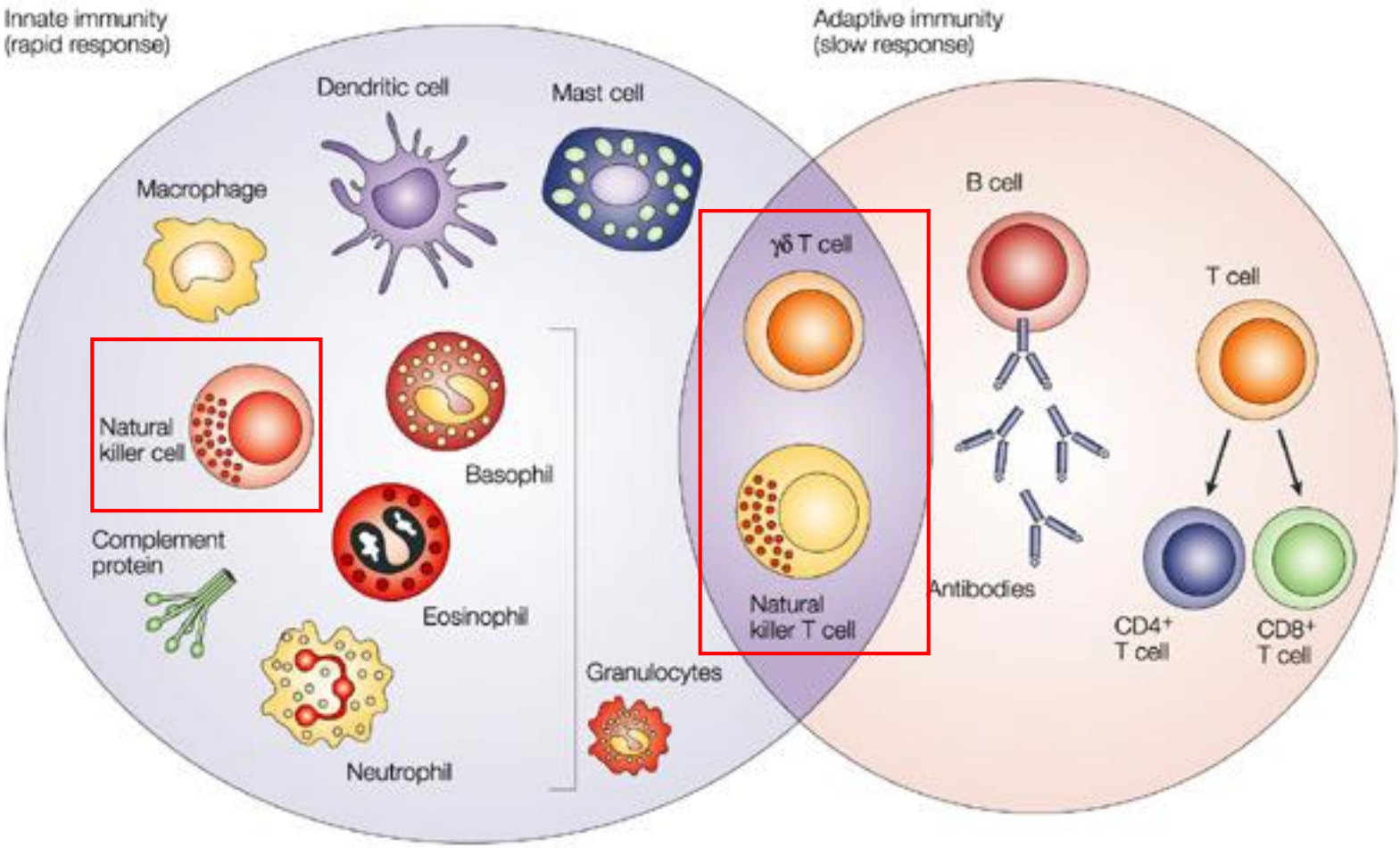
- **Adaptive immunity** adapts to previous experience; Stronger protection following secondary exposure.
- Very large number of distinct “antigen receptors” of T and B lymphocytes;
- generated by DNA rearrangement in each developing lymphocyte;
- clonal selection of lymphocytes recognizing antigen derived from microbe or self

Defining cell lineages within the immune system



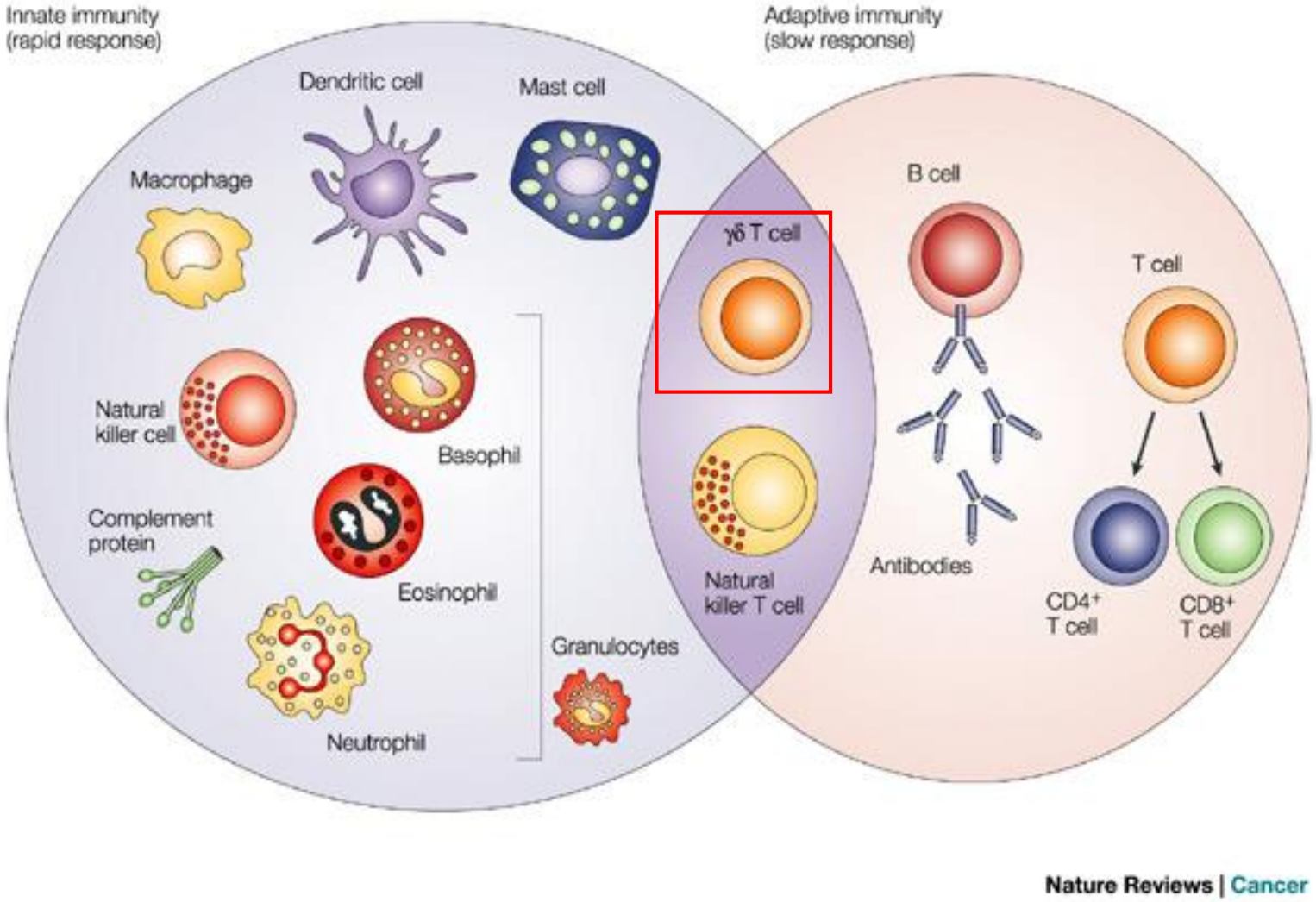
Nature Reviews | Cancer

Innate lymphocytes are comprised of NK cells, NK T cells and γδ T cells



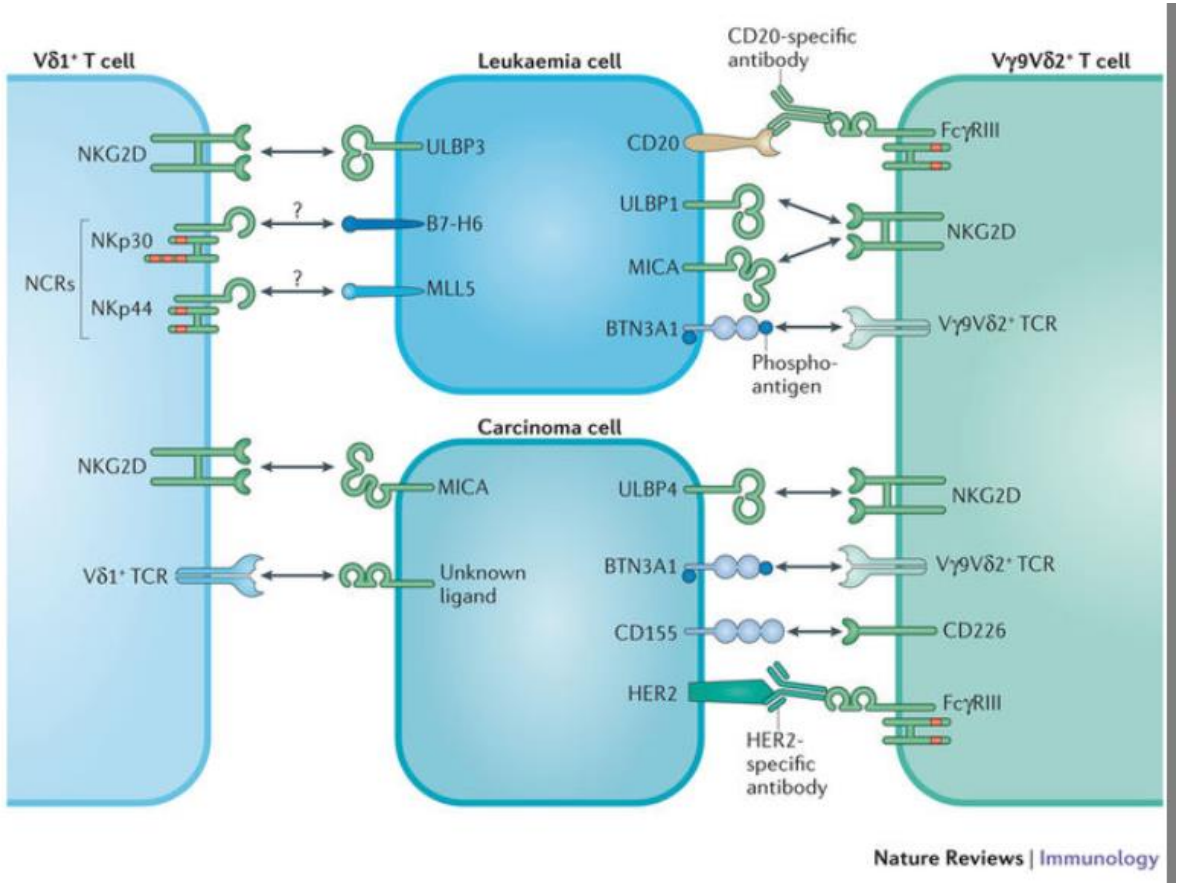
Nature Reviews | Cancer

Lipid-reactive T cells bridge innate and adaptive immunity



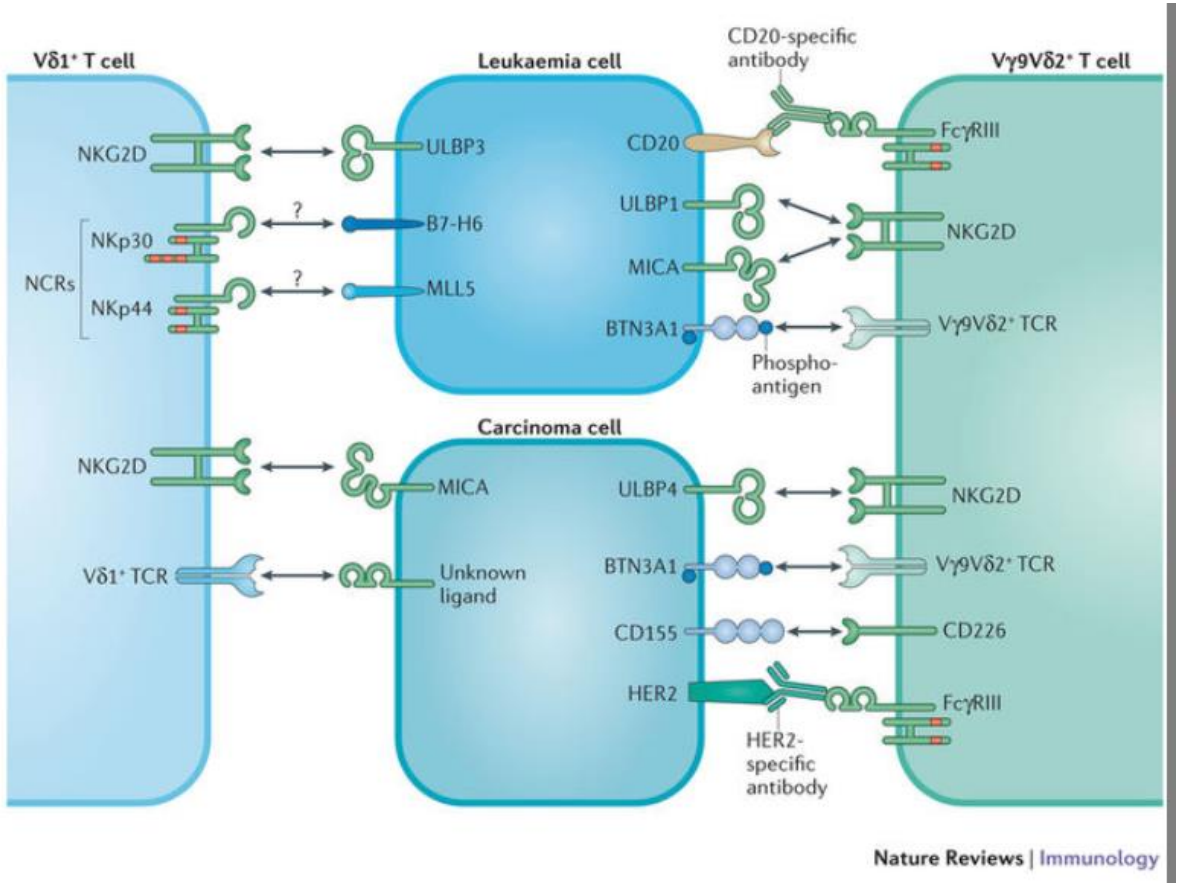
γδ T cell: respond to self- and non-self phospholipid antigens; produce cytokines/chemokines and promote inflammation; promote epithelial growth, wound healing, B cell help, DC maturation and antigen presentation; Th1 or Th17

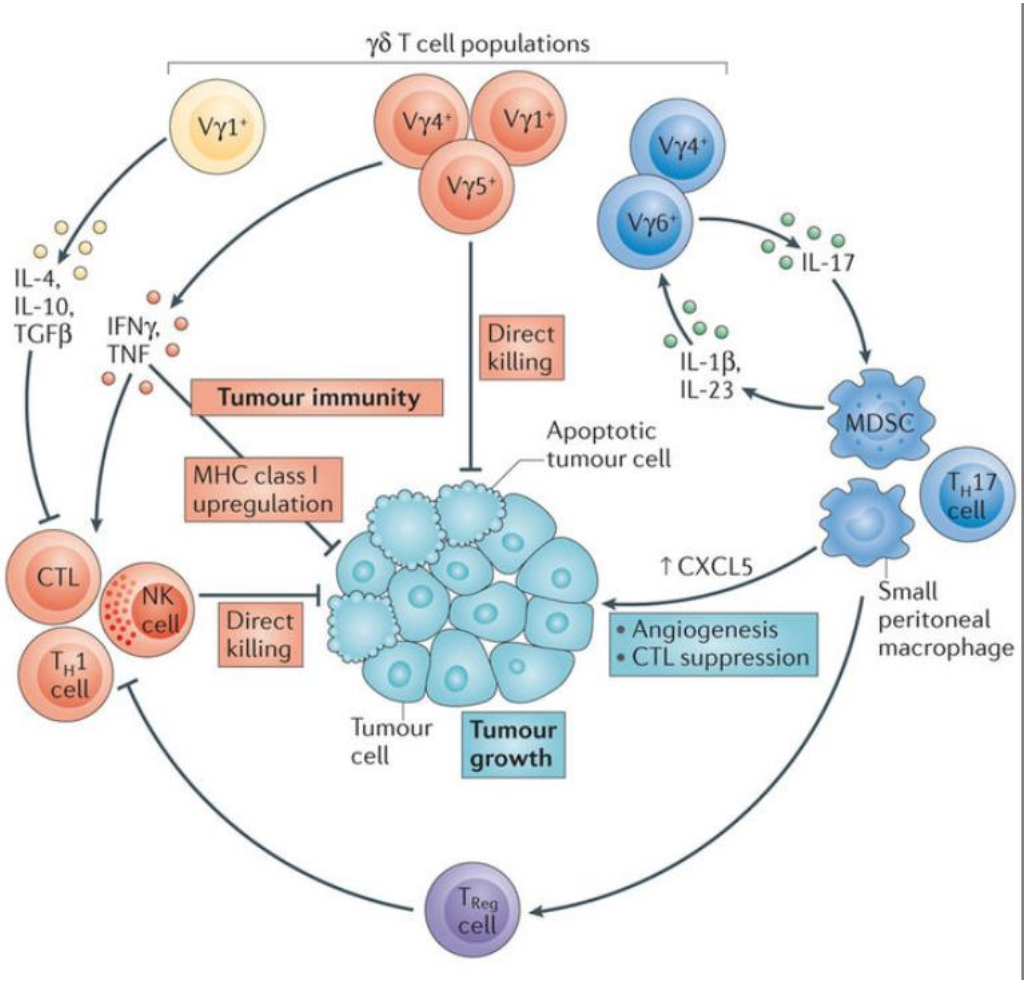
Tumor cell recognition by γδ T cells mediated by receptor-ligand interactions



Silva-Santos, 2015 *Nat rev Immunol*

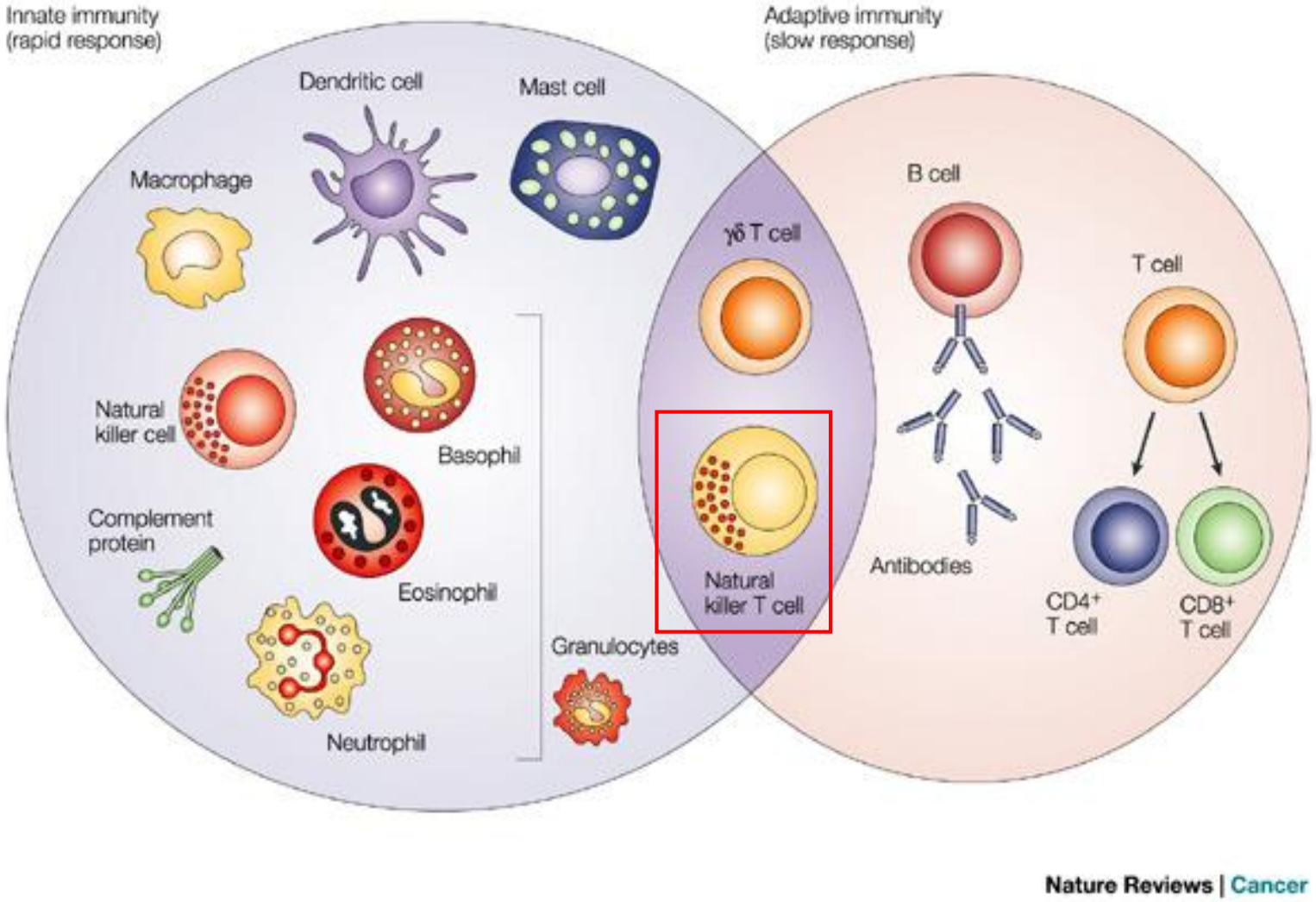
γδ T cells can exert antitumor or protumor roles





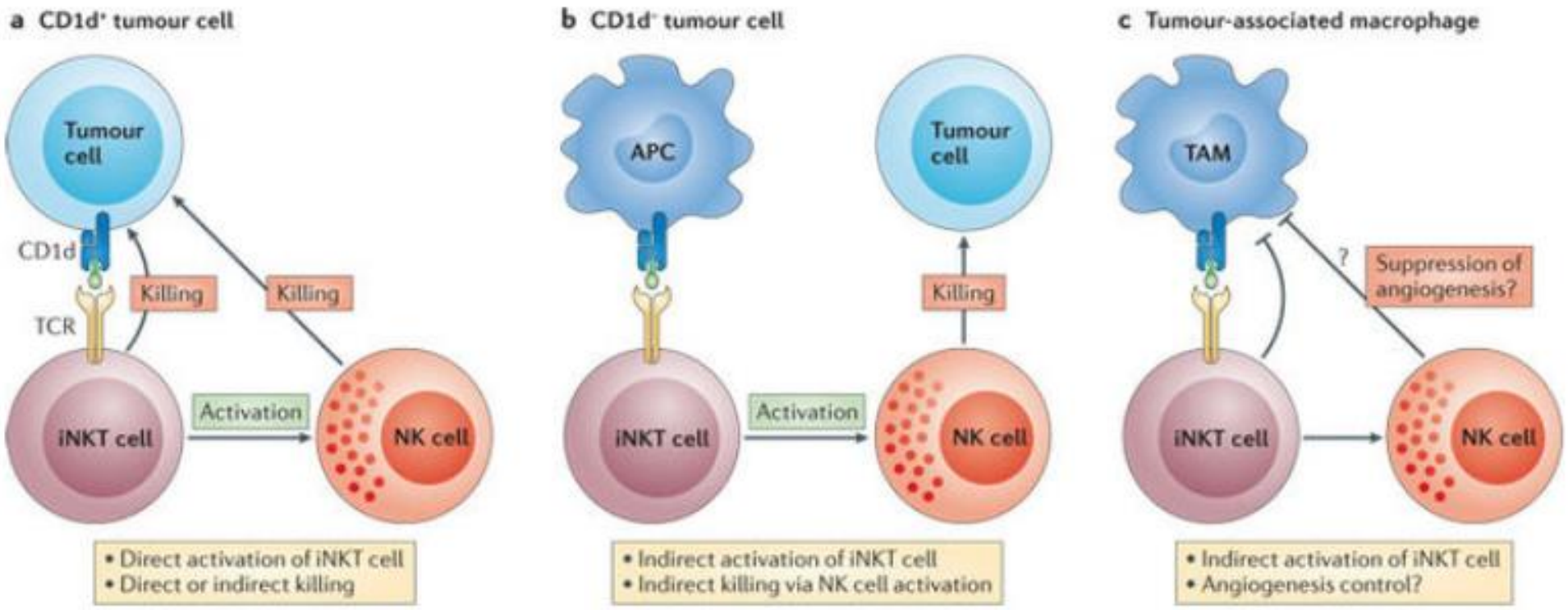
Silva-Santos, 2015 *Nat rev Immunol*

Lipid-reactive T cells bridge innate and adaptive immunity



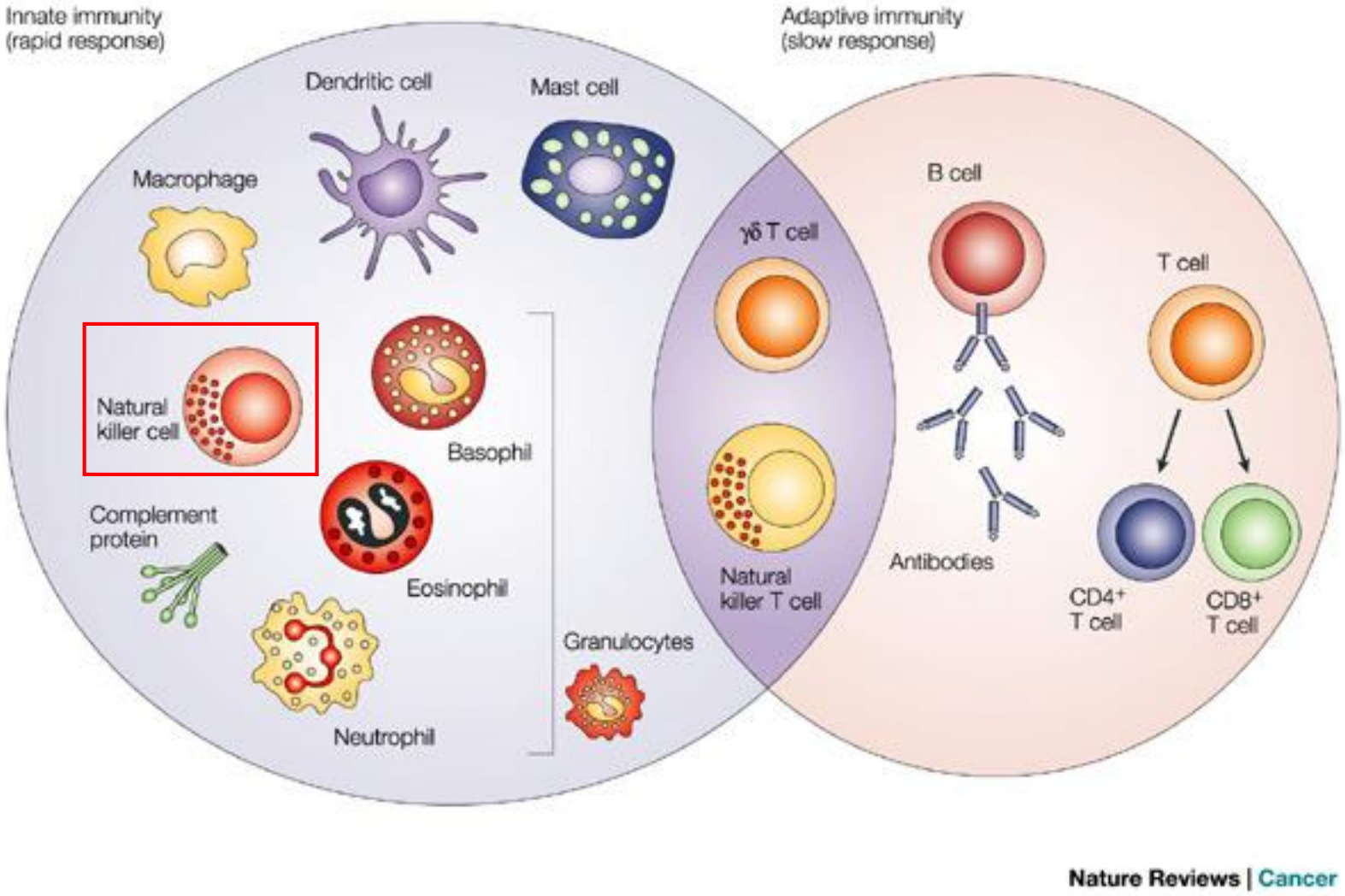
NK T cells: share properties of both NK cells and T cells; respond to both self- and non-self glycolipid antigens presented through CD1d; produce cytokines/chemokines; cytotoxicity ; Th1 or Th2 or Th17

Antitumor activities of NKT cells



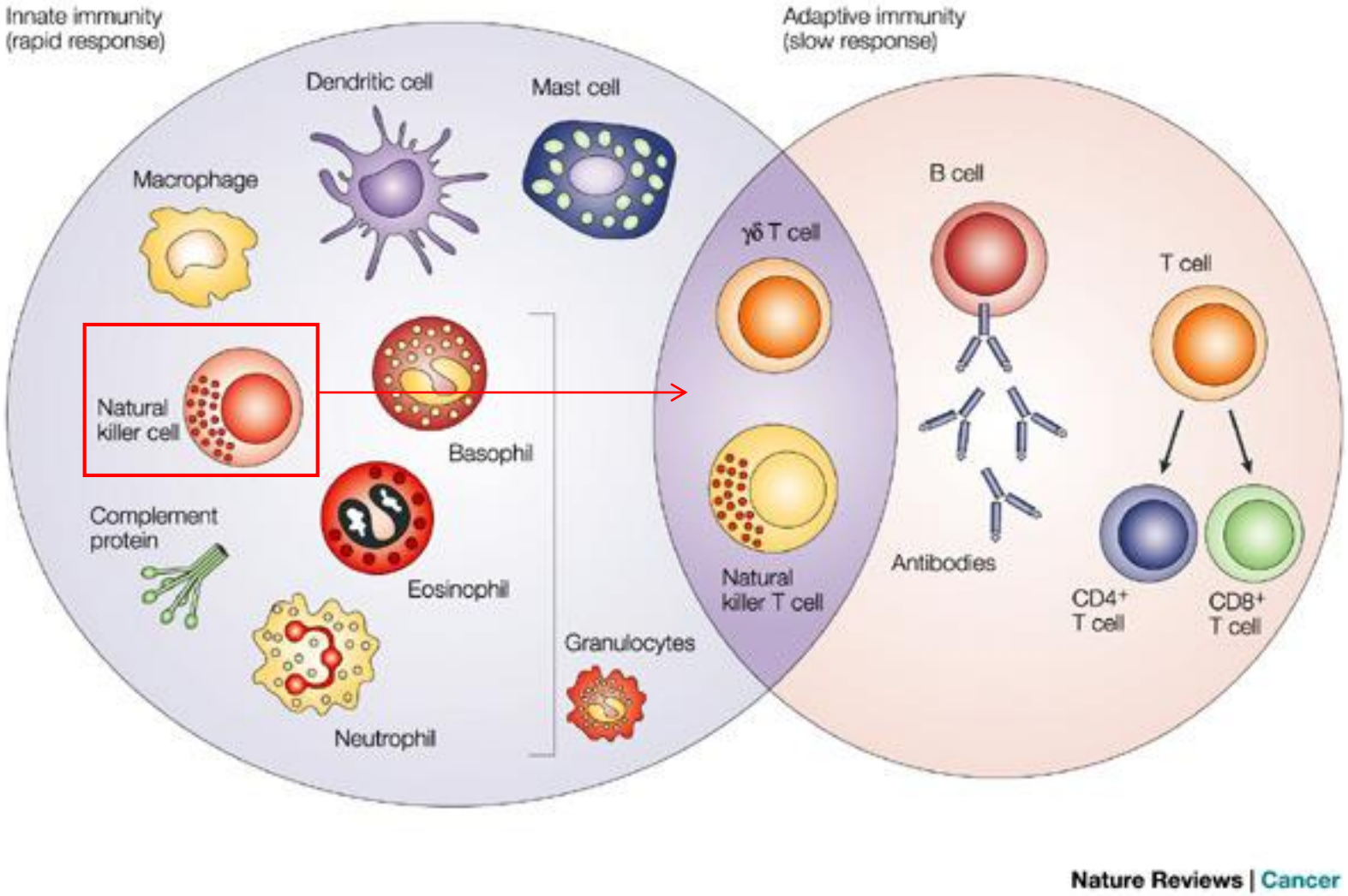
Vivier, 2012 *Nat rev Immunol*

NK cells are an evolutionary predecessor to T cells



NK cells: large, granular cells with pre-formed cytolytic vesicles; sense modulation of HLA class I as well as cytokines, chemokines and activating ligands; defend against 'all' microbes, tumors; critical for vascularization and arterial remodeling; pregnancy and promoting GVL after transplantation

NK cells also have adaptive roles!



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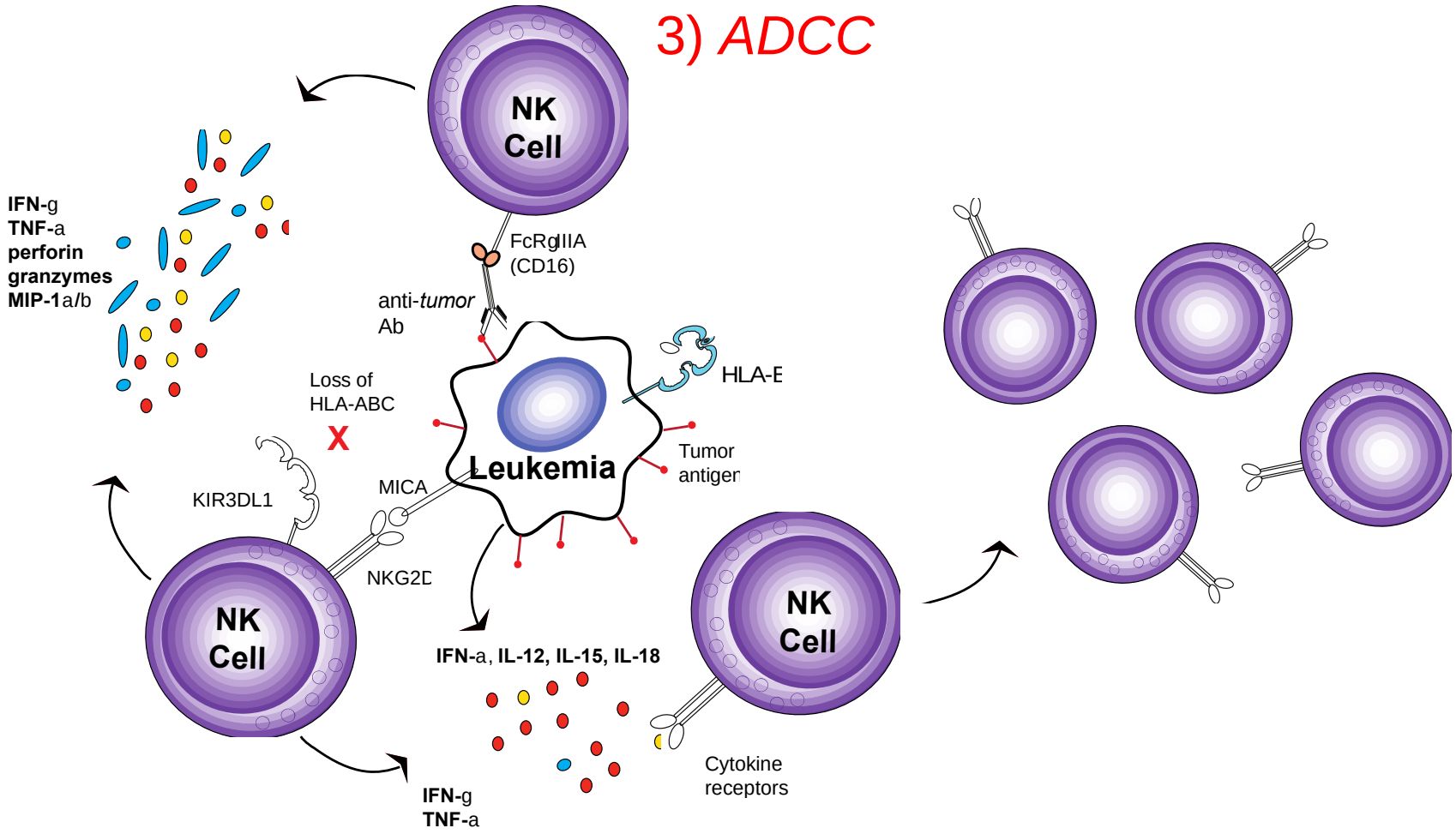
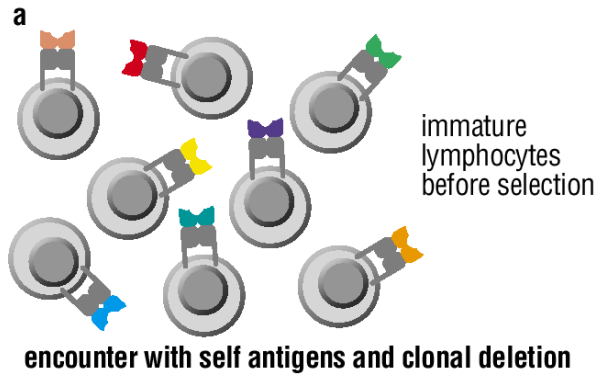
NK cell functions are coordinated across specialized subsets - Example: acute myeloid leukemia (AML)



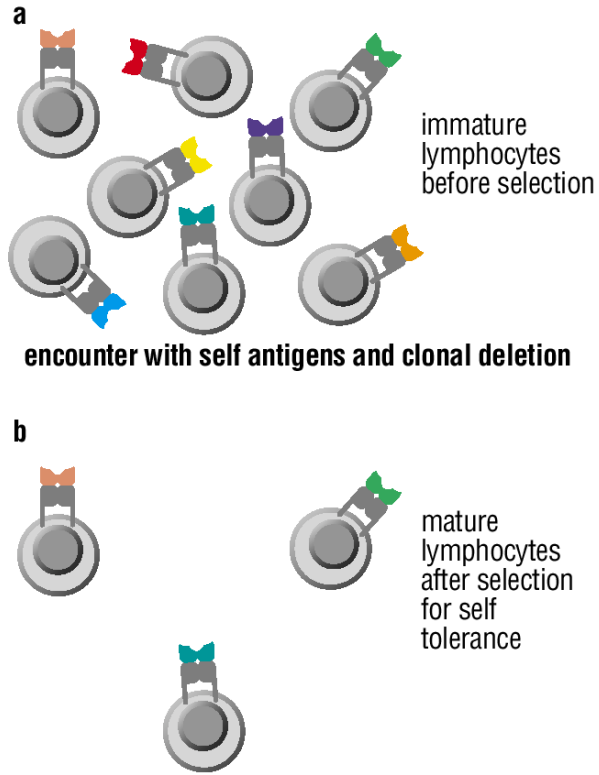
Generation of lymphocytes of many specificities



Clonal Selection of T cells requires innate lymphocytes

Generation of lymphocytes of many specificities

<u>Clonal deletion</u> to remove self-reactive lymphocytes



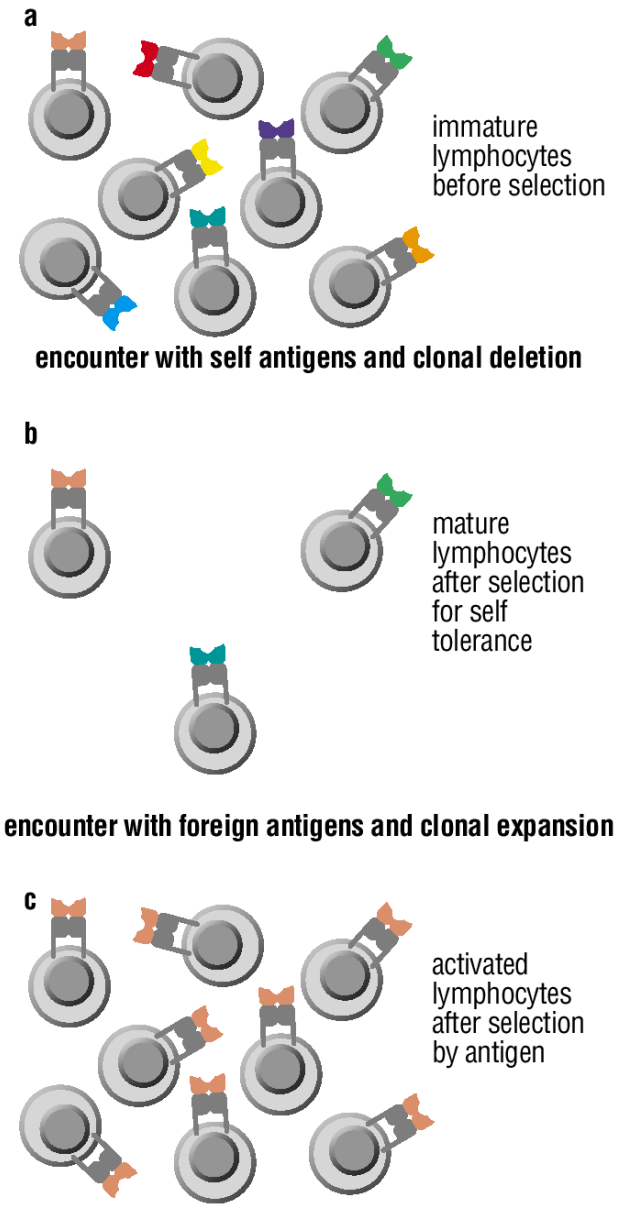
Clonal deletion required for homeostasis… but bad for immunity to infection and against tumors

Generation of lymphocytes of many specificities

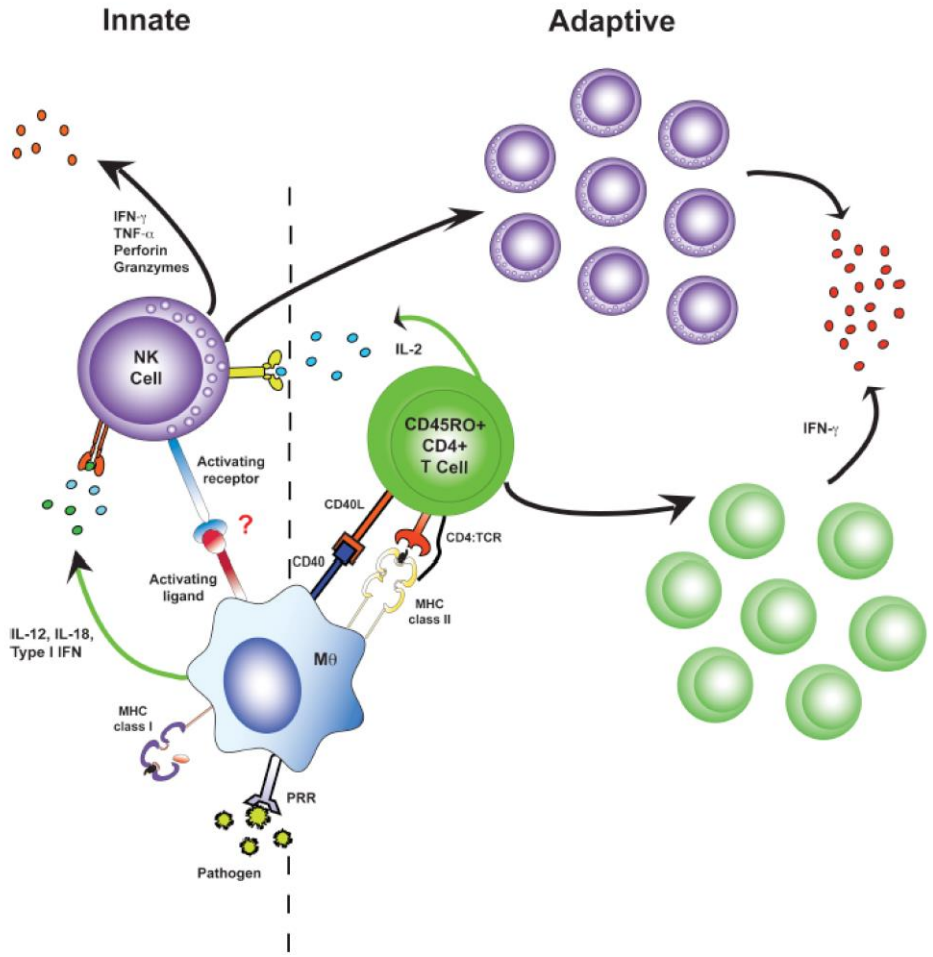
Clonal deletion to remove self-reactive lymphocytes

Clonal expansion requires days to reach sufficient numbers!

Clonal selection to expand pathogen-reactive lymphocytes during an immune response



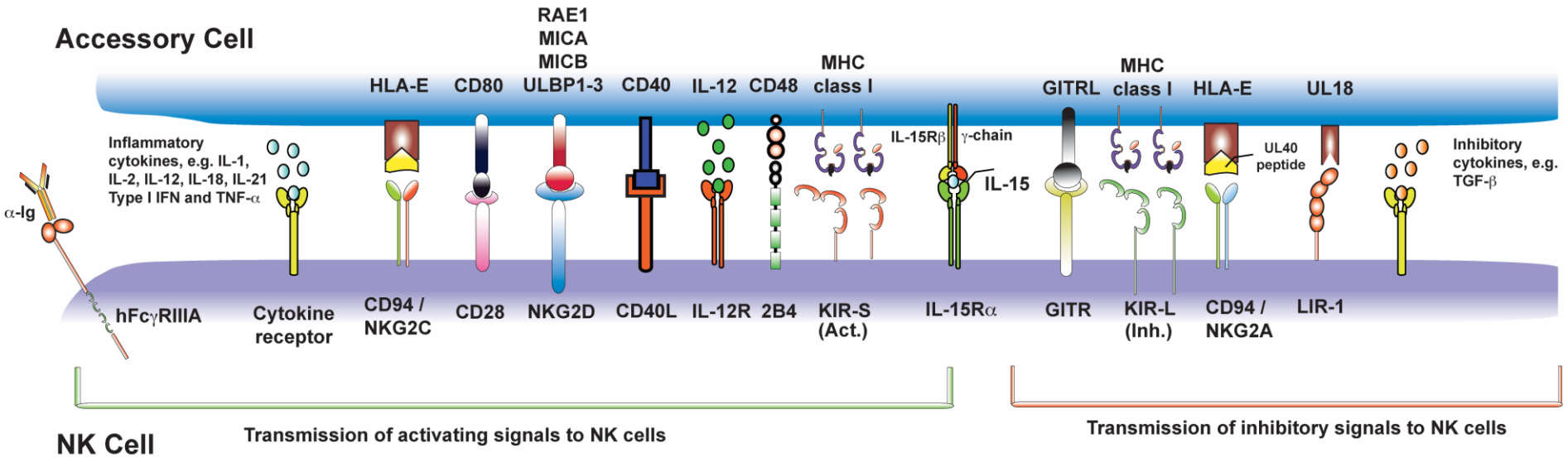
Vaccines harness innate immunity to potentiate immune memory



- Antigen recognition by APC results in expression of activating ligands as well as cytokine production
- Contact-dependent and soluble signals mediate NK cell response
- Critical role for maintaining effector functions until memory cells can expand to sufficient numbers
- 1st example of adaptive roles for human NK cells in vaccine settings to potentiate T cell memory:
  - rabies virus, HBV, malaria
- *Same rules apply for cancer

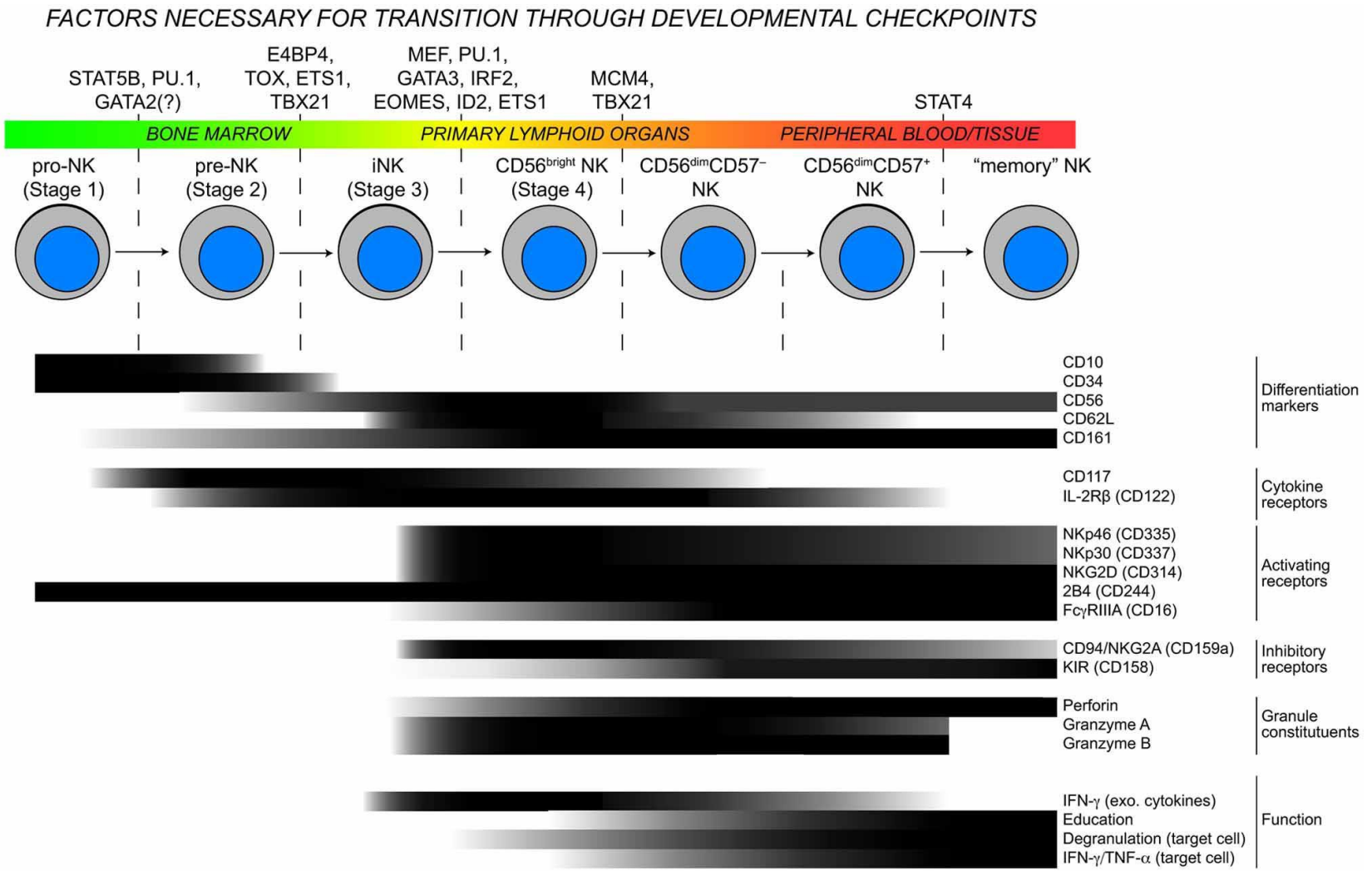
Horowitz, 2010a *J Immunol*
Horowitz, 2010b *J Immunol*
Evans, Horowitz, 2011 *Eur J Im*
Horowitz, 2012 *J Immunol*

NK cell activation is regulated by the collective strength of inhibitory and activating signals



Horowitz, 2012 *Front Immunol*

NK cell functions are acquired, regulated and differentiated as NK cells mature

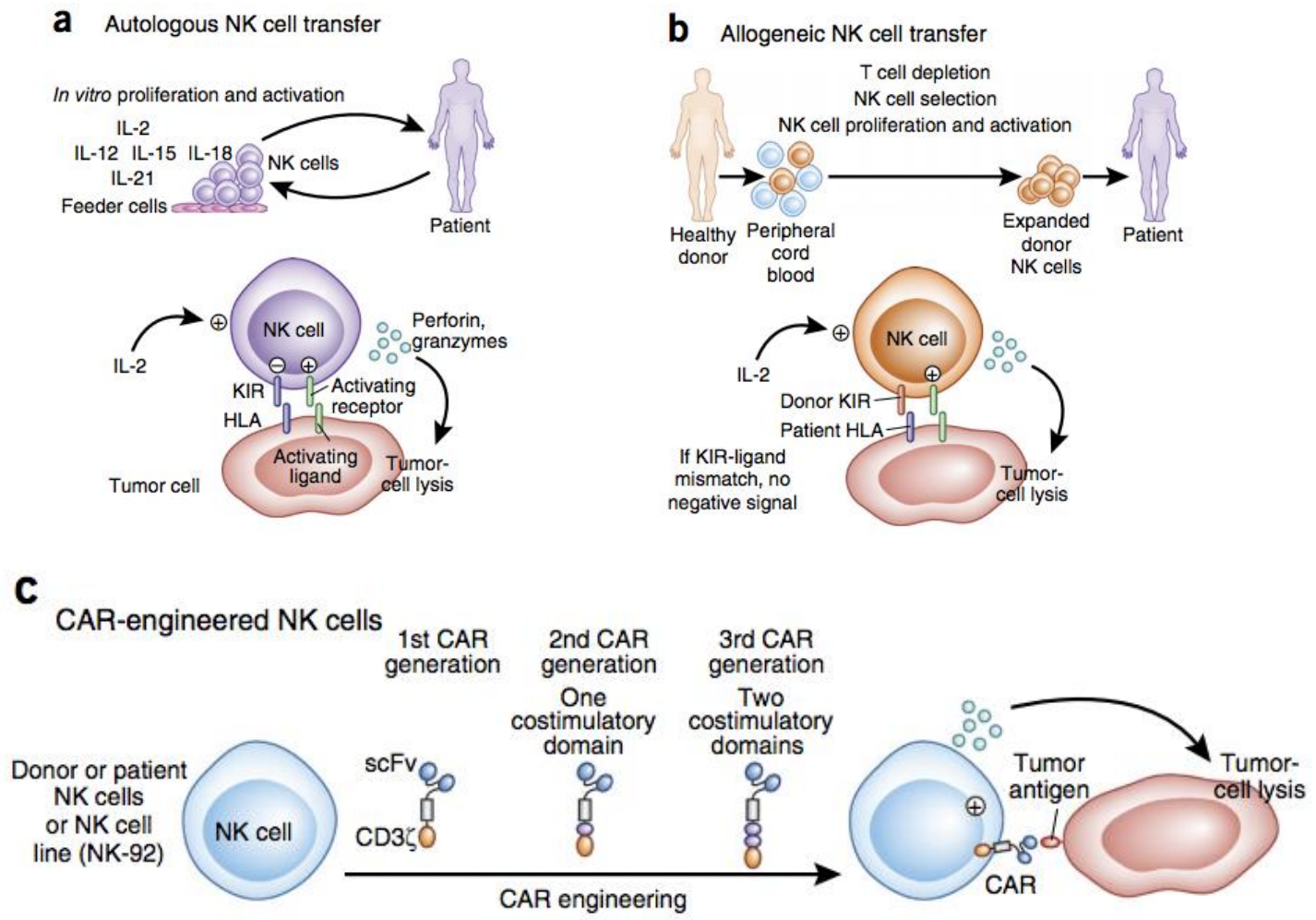


Cichocki, 2013 *Front Immunol*

How can NK cells be harnessed for treatment against cancers?

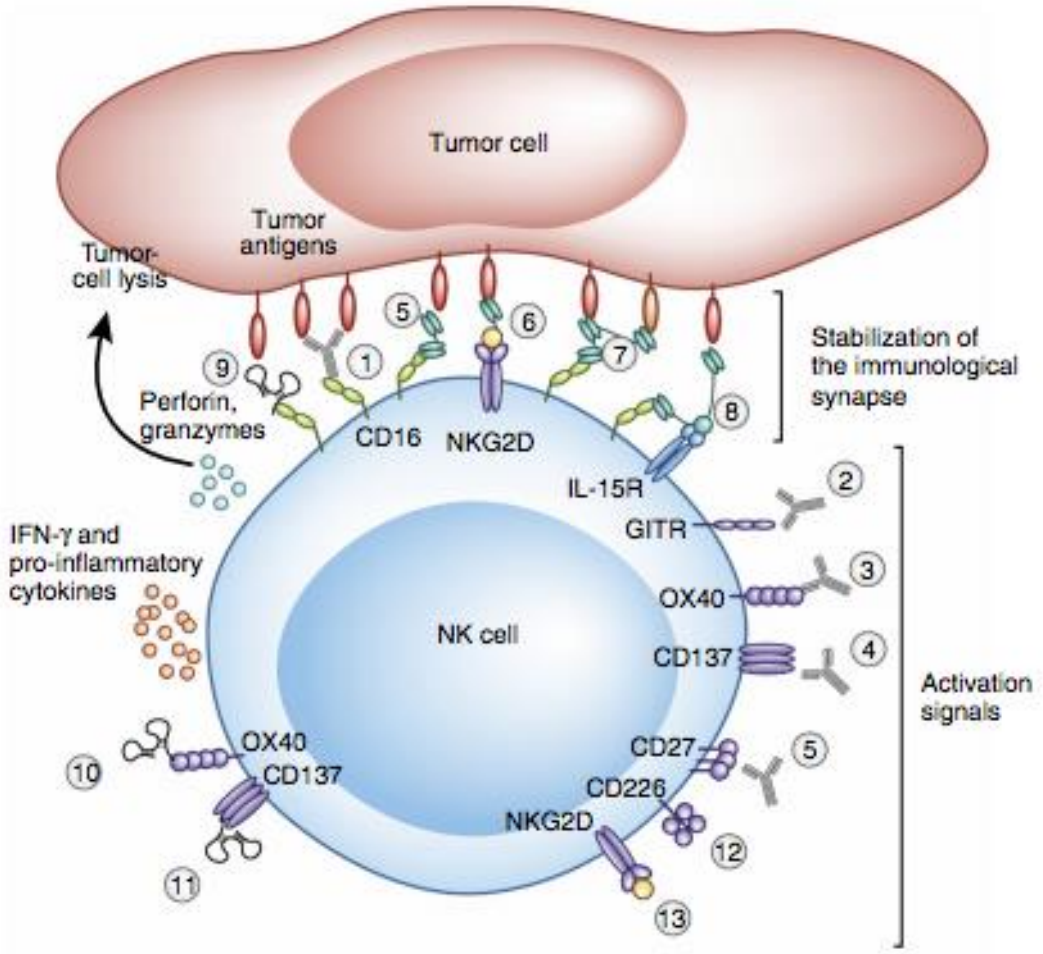
- **Adoptive cell transfer**: autologous; allogeneic; NK cell lines; CAR NK cells
- **Cytokines**: IL-2; IL-15; IL-15SA-IL-15Rα-Su-Fc (ALT-803)
- **Anti-cancer agents**: IMiDs; Bortezomib and genotoxic agents; GSK3 inhibitors
- **Targeting immune-suppressive pathways**: Treg depletion; TGF-β blockade
- **Agonists of NK-cell activating receptors**: tumor-targeting mAbs; BiKEs and TriKEs; mAbs to CD137
- **Checkpoint inhibition**: mAbs to KIRs (IPH2101 and Lirilumab); mAbs to NKG2A (monalizumab)

Adoptive NK cell transfer therapies



Guillerey, 2016 *Nat Rev Immunol*

Therapies targeting activating NK receptors



FDA approved

1. Tumor-antigen-specific mAb

Clinical trials

2. mAb to GITR (TRX518)
3. mAb to OX40 (MEDI6469, MEDI6383, MOXR0916)
4. mAb to CD137 (urelumab, PFZ-05082566)
5. mAb to CD27 (varlilumab)

Preclinical development

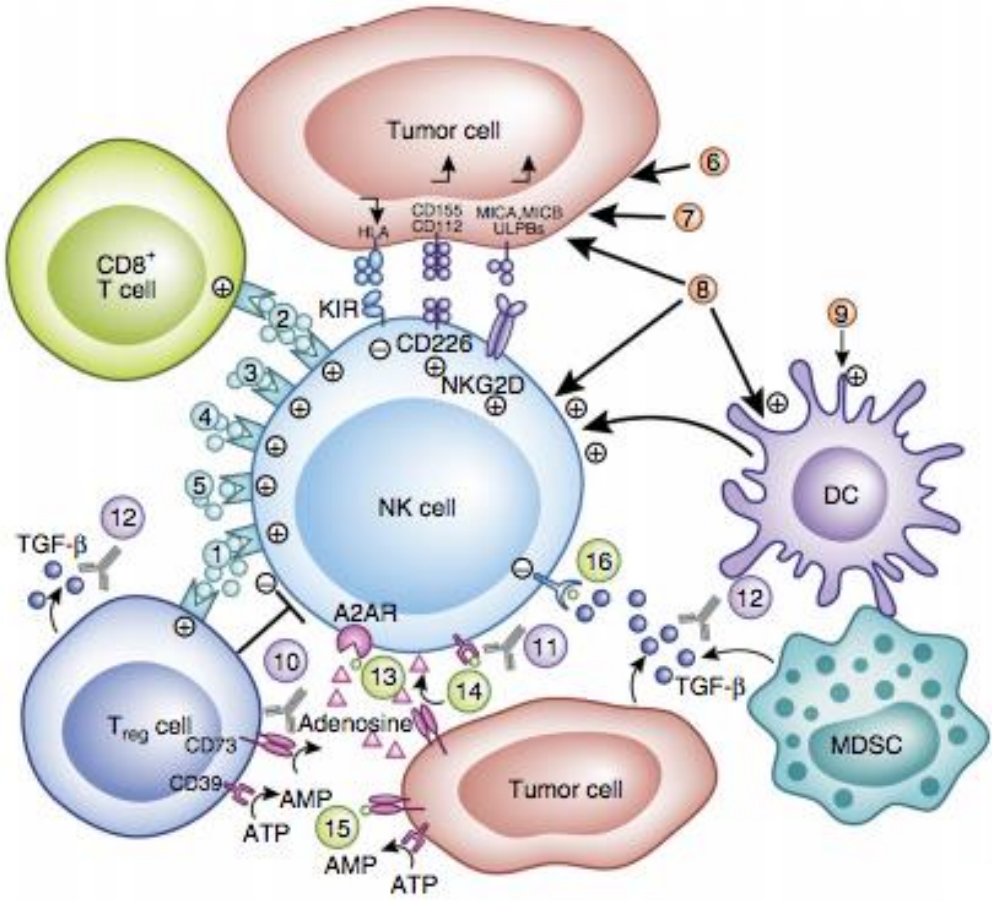
5. BiKE
6. NKG2D ligand–antitumour Fv fusion
7. TriKE that binds two different tumor antigens
8. TriKE that incorporates IL-15
9. Bispecific aptamer
10. OX40 agonistic aptamer
11. CD137 agonistic aptamer

Not developed yet

12. CD226 agonist
13. Soluble activating NKG2D ligand

Guillerey, 2016 *Nat Rev Immunol*

Therapies targeting activating cytokines, chemotaxic agents and Abs abrogating inhibitory signals



Activating cytokines

1. IL-2
2. IL-15
3. IL-12
4. IL-18
5. IL-21

Blocking antibodies

10. mAb to CD73
11. mAb to CD39
12. TGF-β-neutralizing mAb

Chemotherapeutics

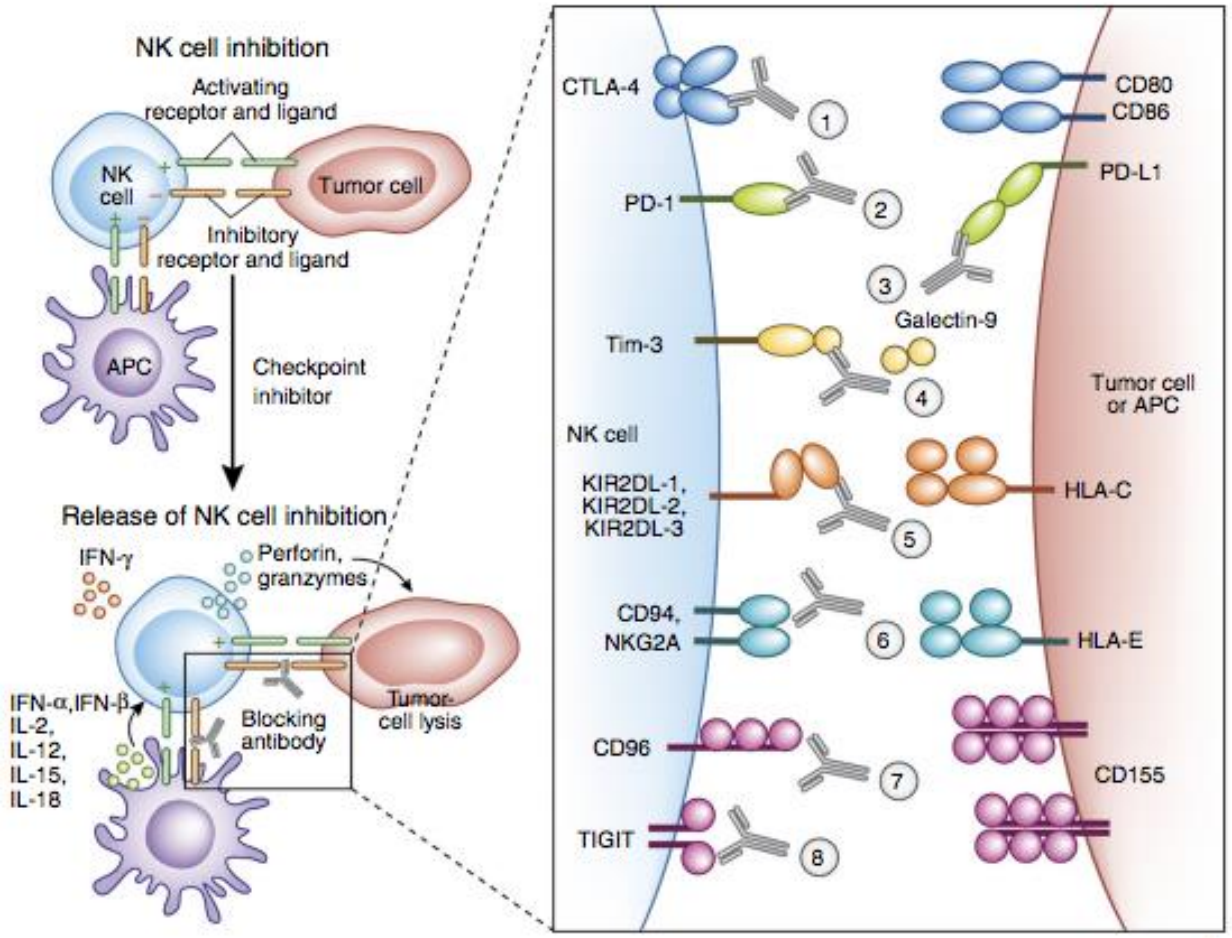
6. Genotoxic drugs (demythelating agents, histone deacetylases)
7. Proteasome inhibitors (bortezomib)
8. IMiDs (lenalidomide, pomalidomide)
9. Imatinib

Small-molecule inhibitors

13. A2A receptor antagonist (PBF-509)
14. CD39 inhibitor (POM-1)
15. CD73 inhibitor (APCP)
16. TGF-β receptor inhibitor

Guillerey, 2016 *Nat Rev Immunol*

Therapies targeting checkpoint inhibitors



FDA approved

1. mAb to CTLA-4 (ipilimumab)
2. mAb to PD-1 (nivolumab or pembrolizumab)

Clinical trials

3. mAb to PD-L1 (atezolizumab)
4. mAb to Tim-3 (MBG453)
5. mAb to a KIR (1-7F9 (IPH2101) or lirilumab (IPH2102))
6. Anti-NKG2A (monalizumab (IPH2201))

Preclinical development

7. mAb to CD96
8. mAb to TIGIT

Guillerey, 2016 *Nat Rev Immunol*

Lessons and Take Home Messages

- Innate lymphocytes bridge the innate and adaptive immune responses
- Collectively survey environment for cell-surface bound and soluble stimuli as well as for modulation of HLA class I molecules
- NK cells display broad range of effector functions that are mediated by specialized subsets defined along axes of maturation and education
- NK cell activation is regulated through the collective strength of activating and inhibitory signals
- Innate lymphocytes are critical for amplifying and sustaining inflammation until antigen-specific T cells and B cells expand to sufficient numbers
- Innate lymphocytes are increasing focus for immunotherapies as strategy for tumor killing and potentiating memory T cells and B cells