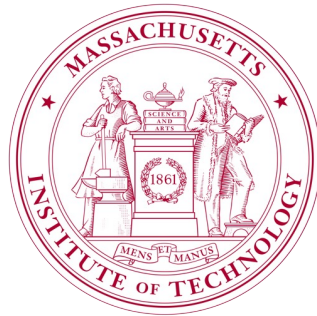


# CAR-NK Cell Therapies for Cancer

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Koch Institute for Integrative Cancer Research  
Department of Biology  
Massachusetts Institute of Technology



# Challenges for CAR-T cell therapies



Rizwan Romee  
Dana-Farber Cancer Institute

- Toxicities

- Cytokine Release Syndrome
- Neurotoxicity
- GVHD
- On-target, off-tumor toxicities

- Relapse

- Loss of target antigen expression
- Limited persistence of CAR-T cells

- Limited efficacy in solid tumors

- Appropriate target antigens
- Limited persistence of CAR-T cells
- Immune suppressive tumor microenvironment

- Cost

- Individualized therapy

- NK cells

- Target tumor-driver mutations

- Memory-like NK cells

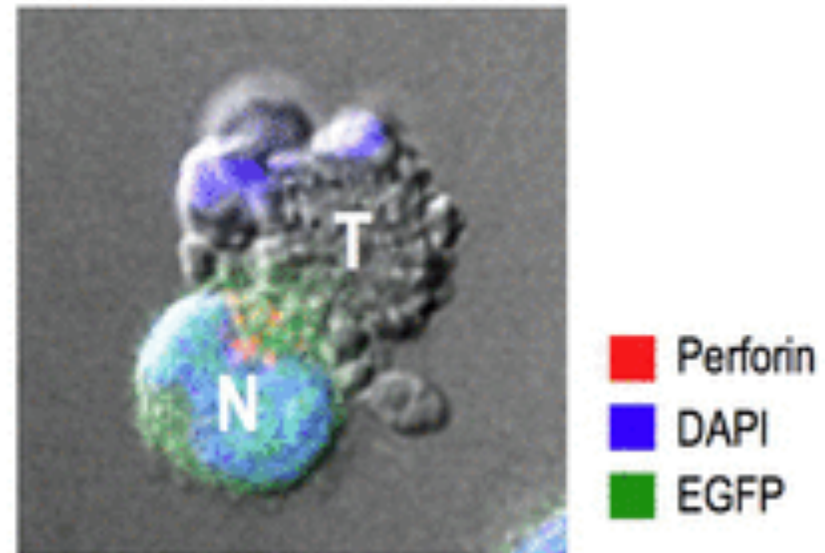
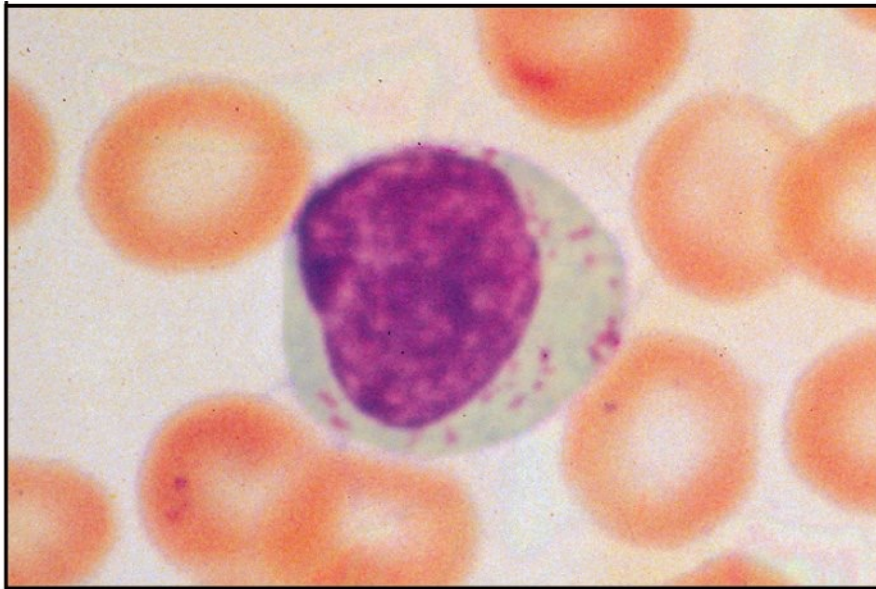
- Induce endogenous immune responses

- Allogeneic NK cells

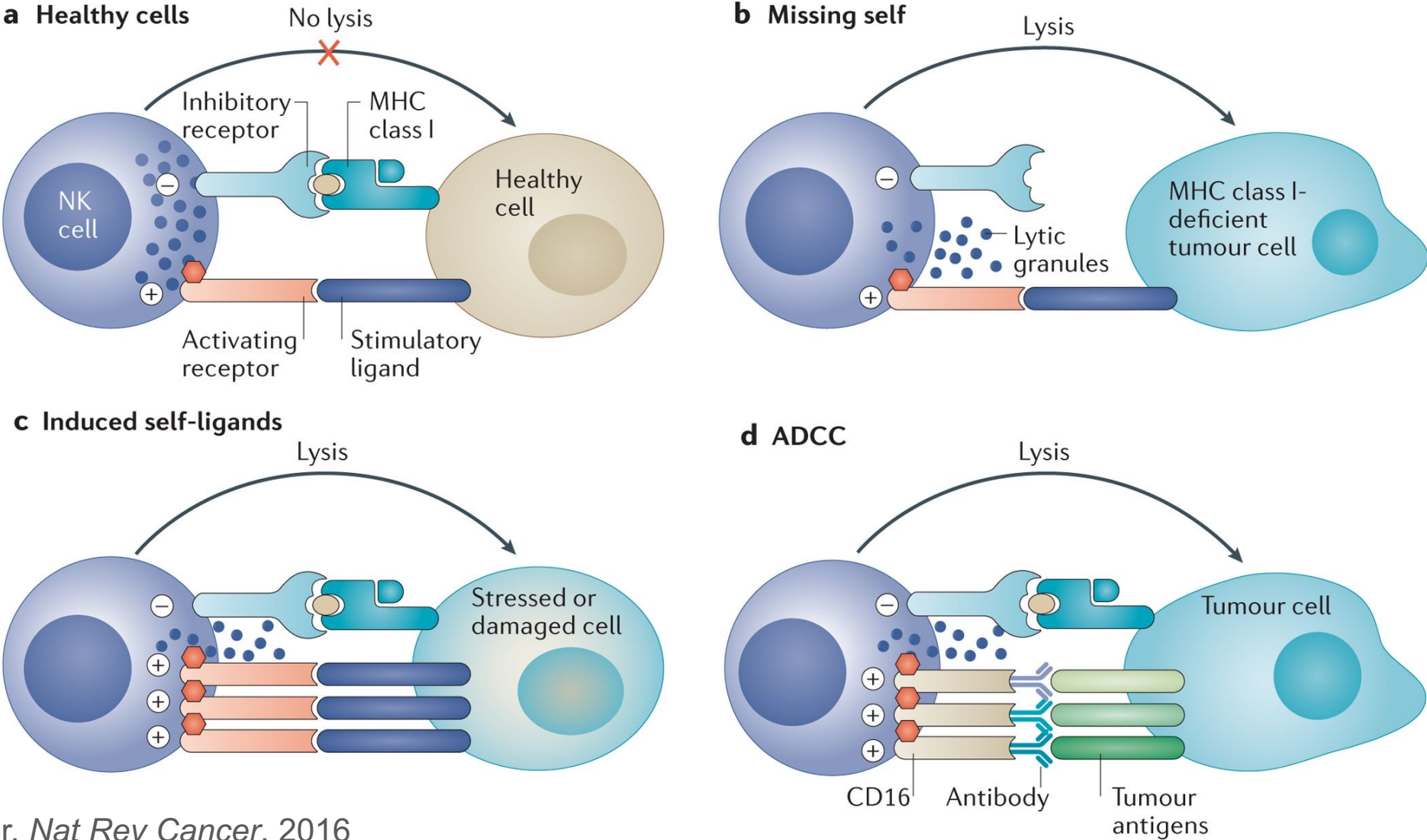
- In vivo CAR transduction

# Natural killer (NK) cells kill altered self-cells by inducing apoptosis

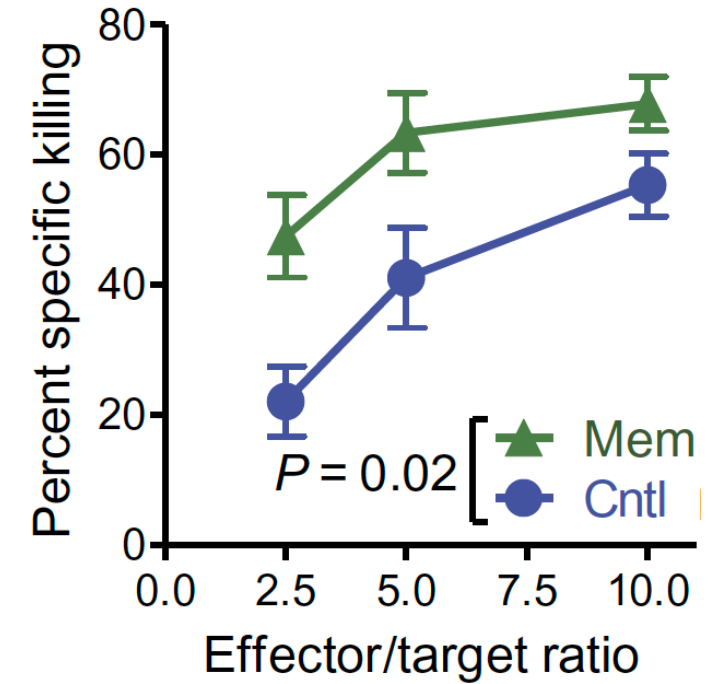
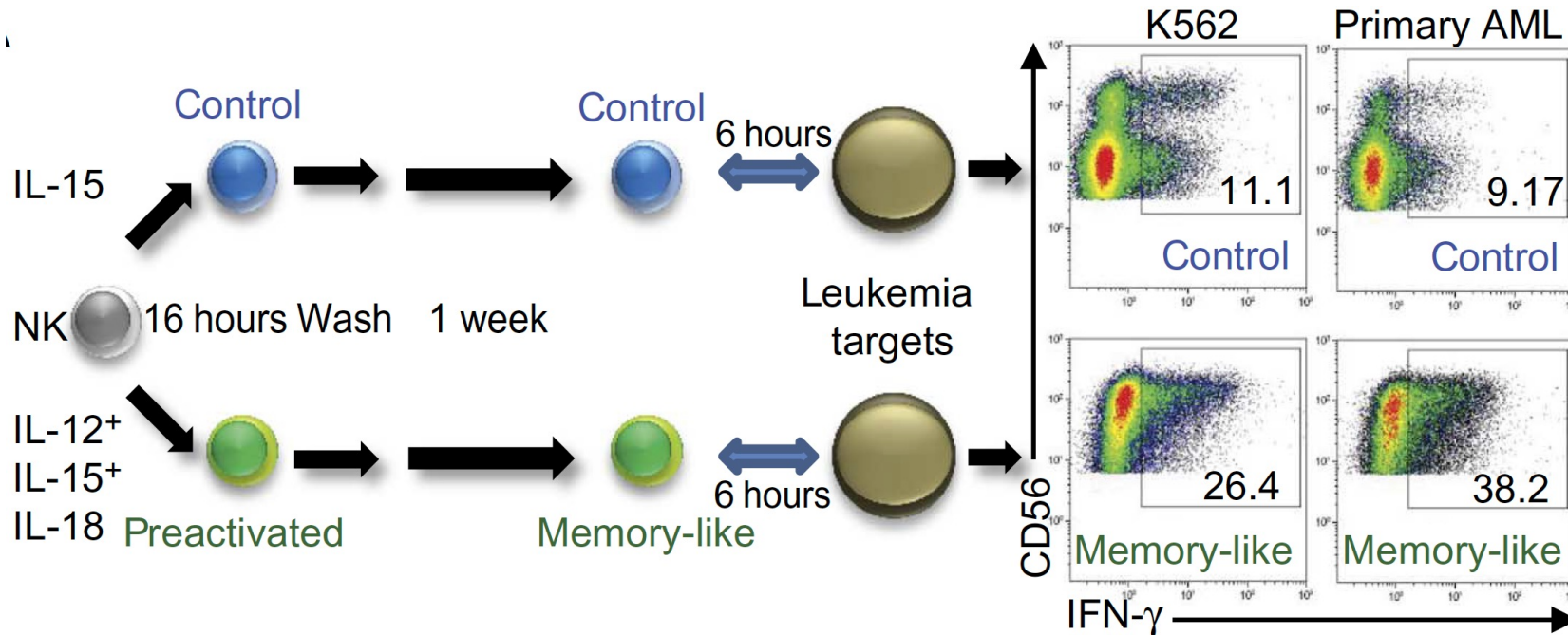
- Virus-infected cells
- Stressed cells
- Tumor cells with no or reduced MHC expression



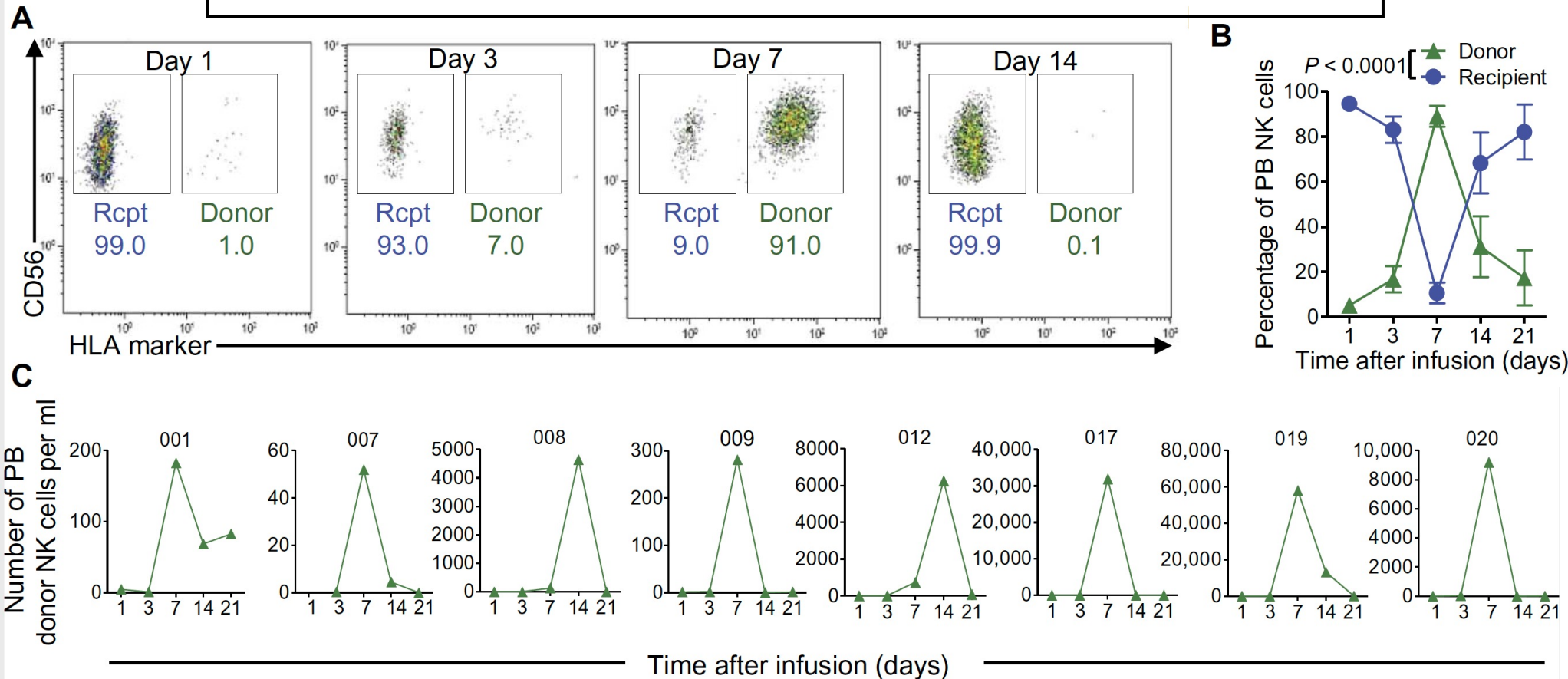
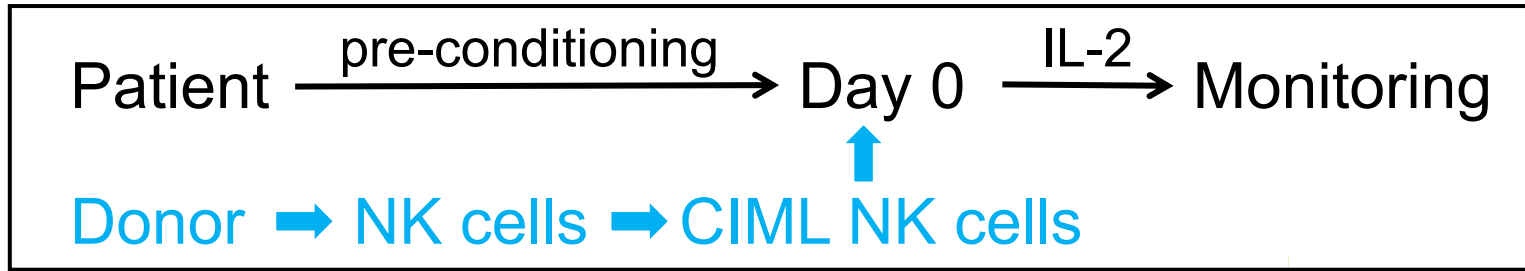
# Activating and inhibitory receptor signaling controls NK cell cytotoxic activity



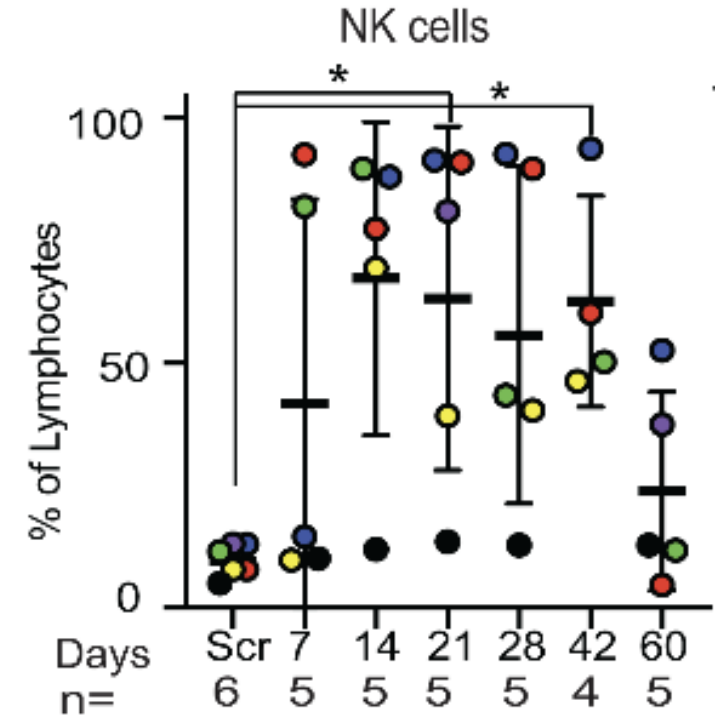
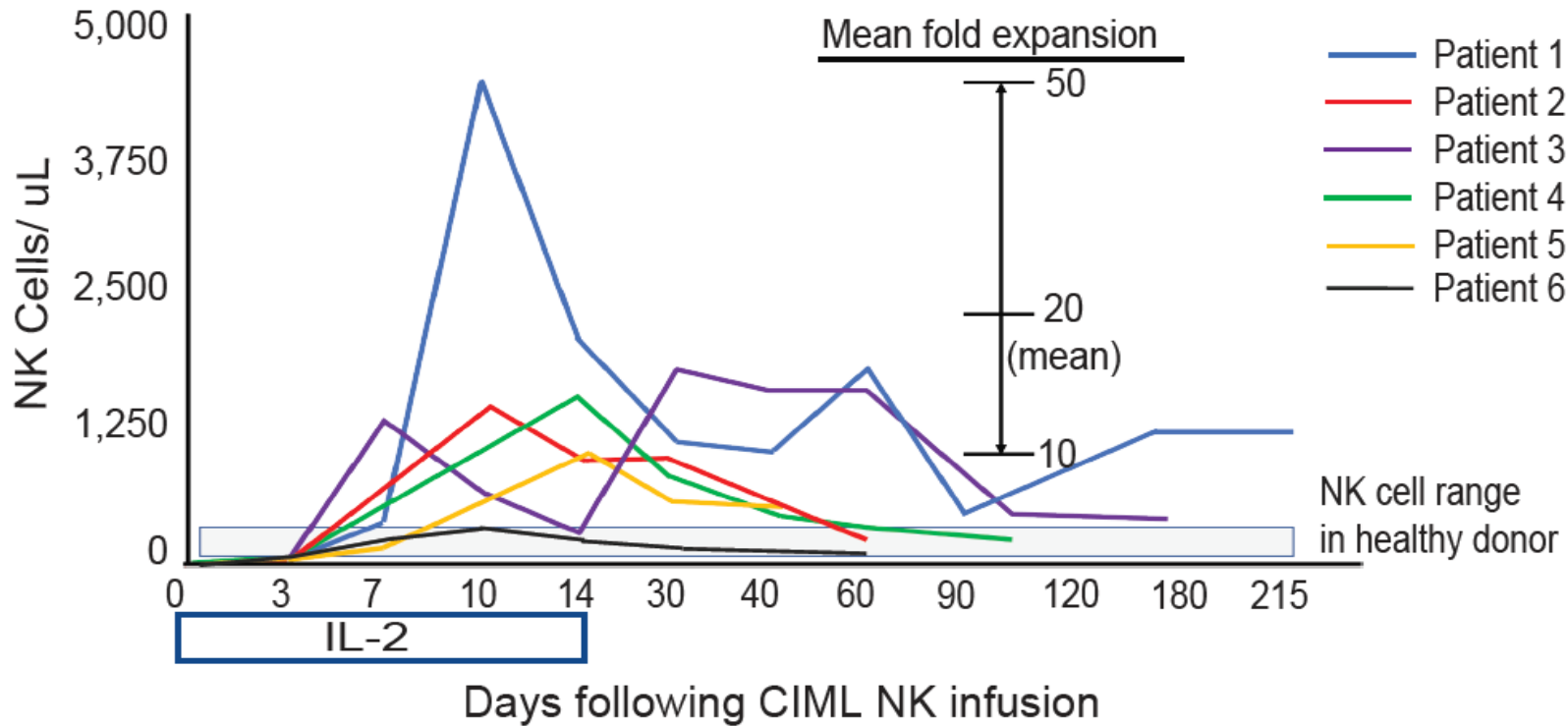
# Cytokine-induced memory-like (CIML) NK cells



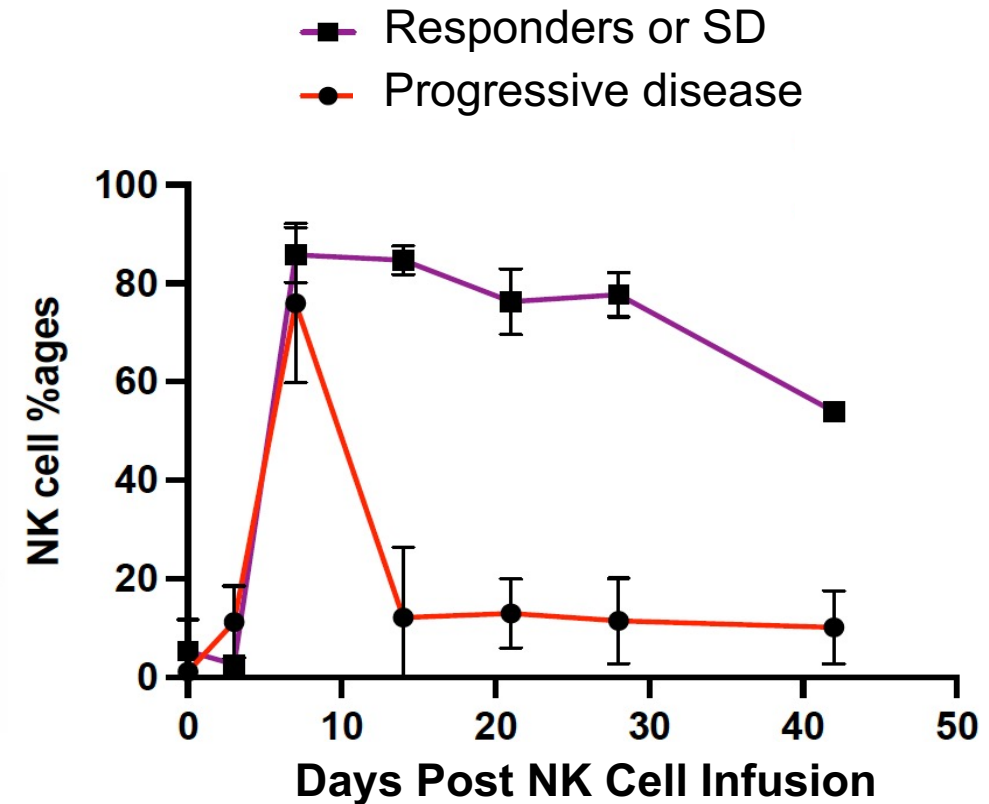
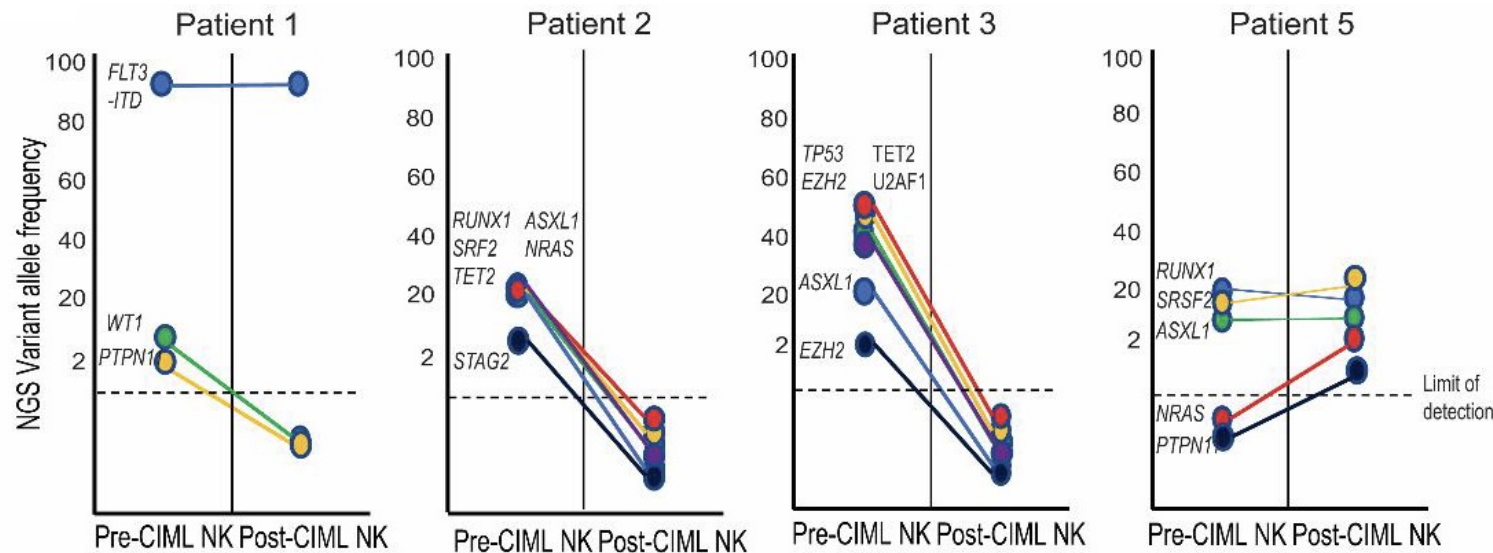
# Transient expansion and persistence of CIML NK cells in allogeneic AML patients



# Prolonged expansion and persistence of CIML NK cells in HLA-matched AML patients



# Clinical response is correlated with persistence of CIML NK cells



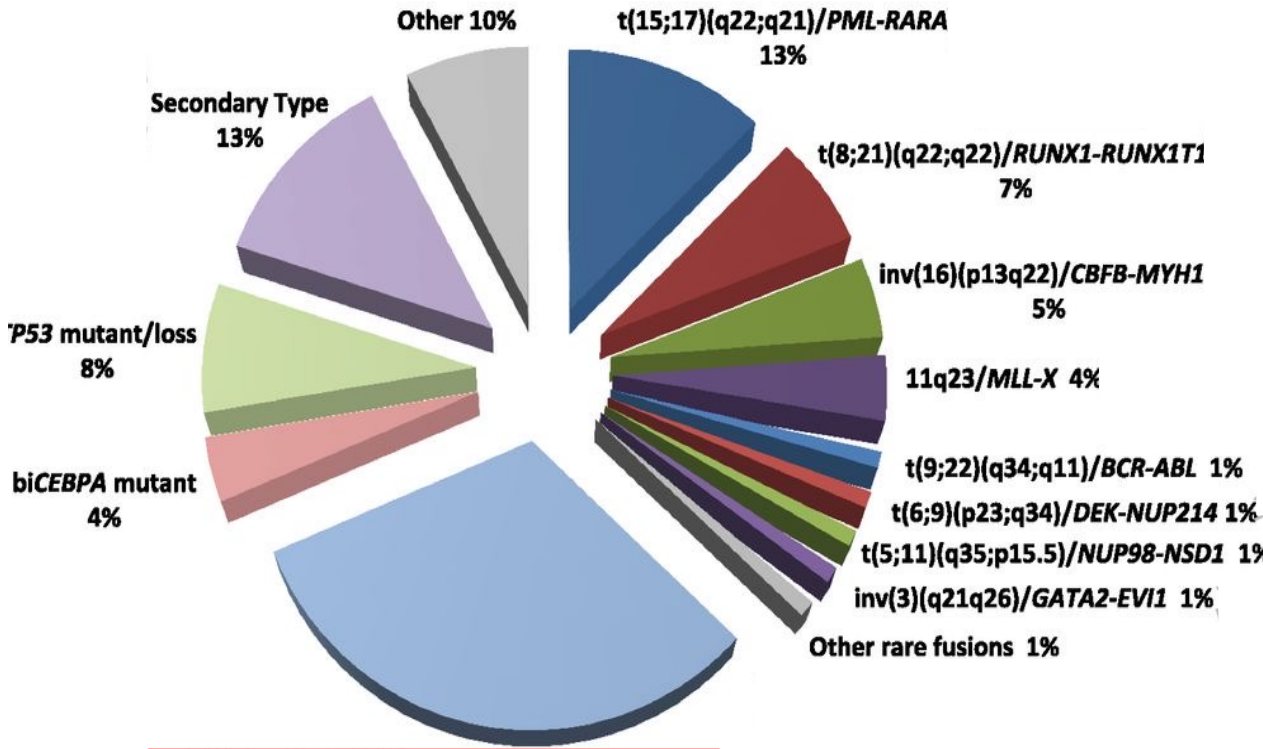


# Nucleophosmin (NPM1) mutation drives the development of acute myeloid leukemia (AML)

WT NPM1: C F R M T D Q E A I Q D L W Q W R K S L \*

NPM1c: C F R M T D Q E **A I Q D L C L A V E E V S L R K** \*

Neoantigen presented by HLA-A\*0201



**NPM1 mutant 33%**

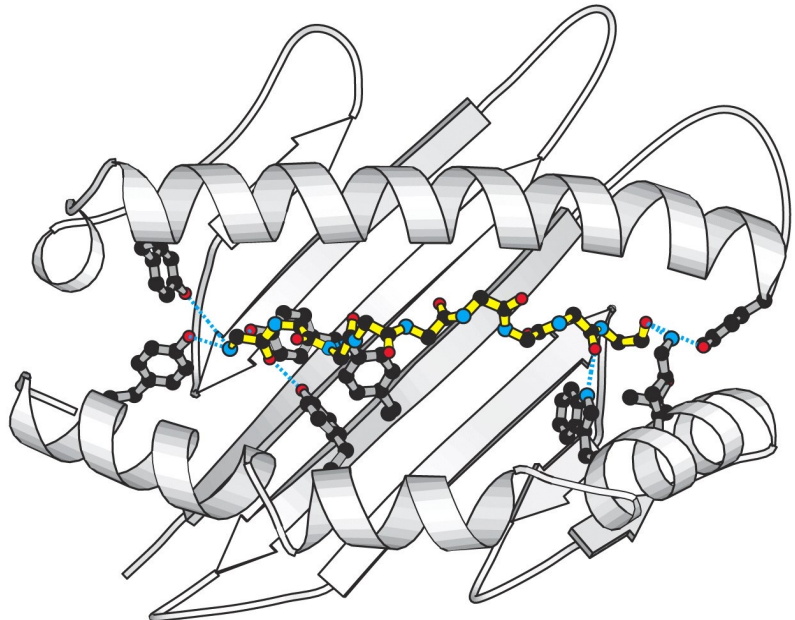
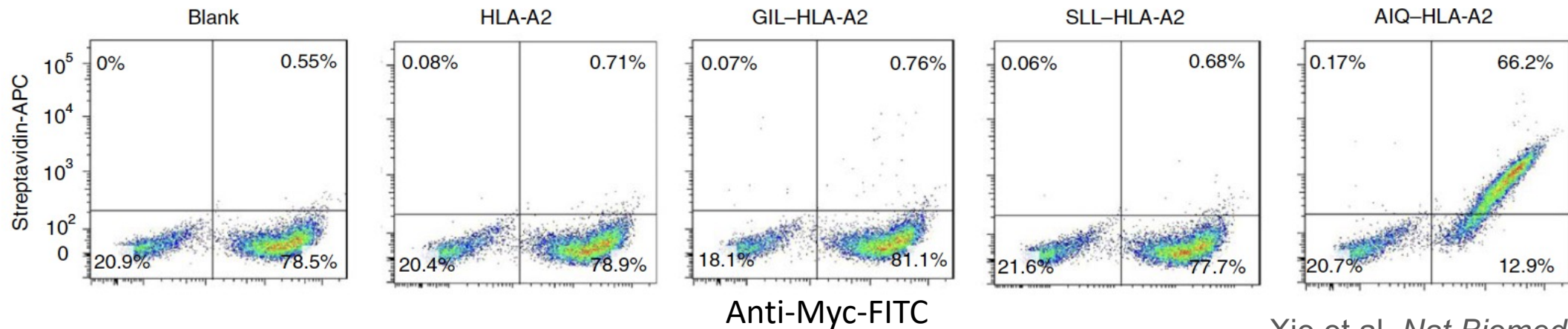
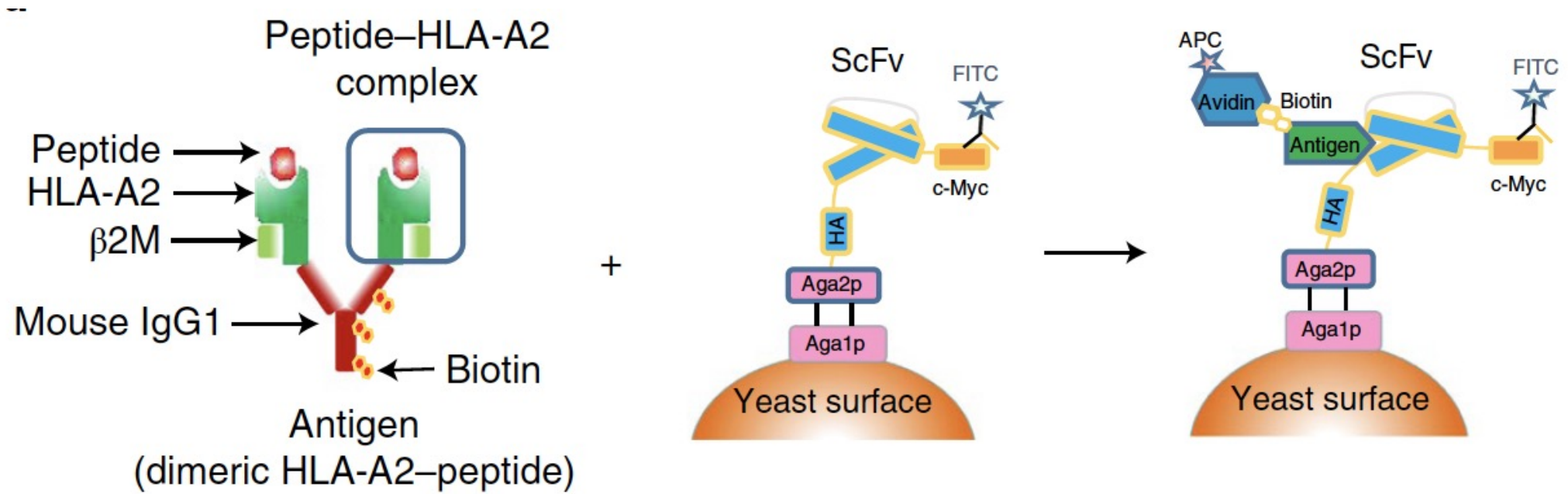
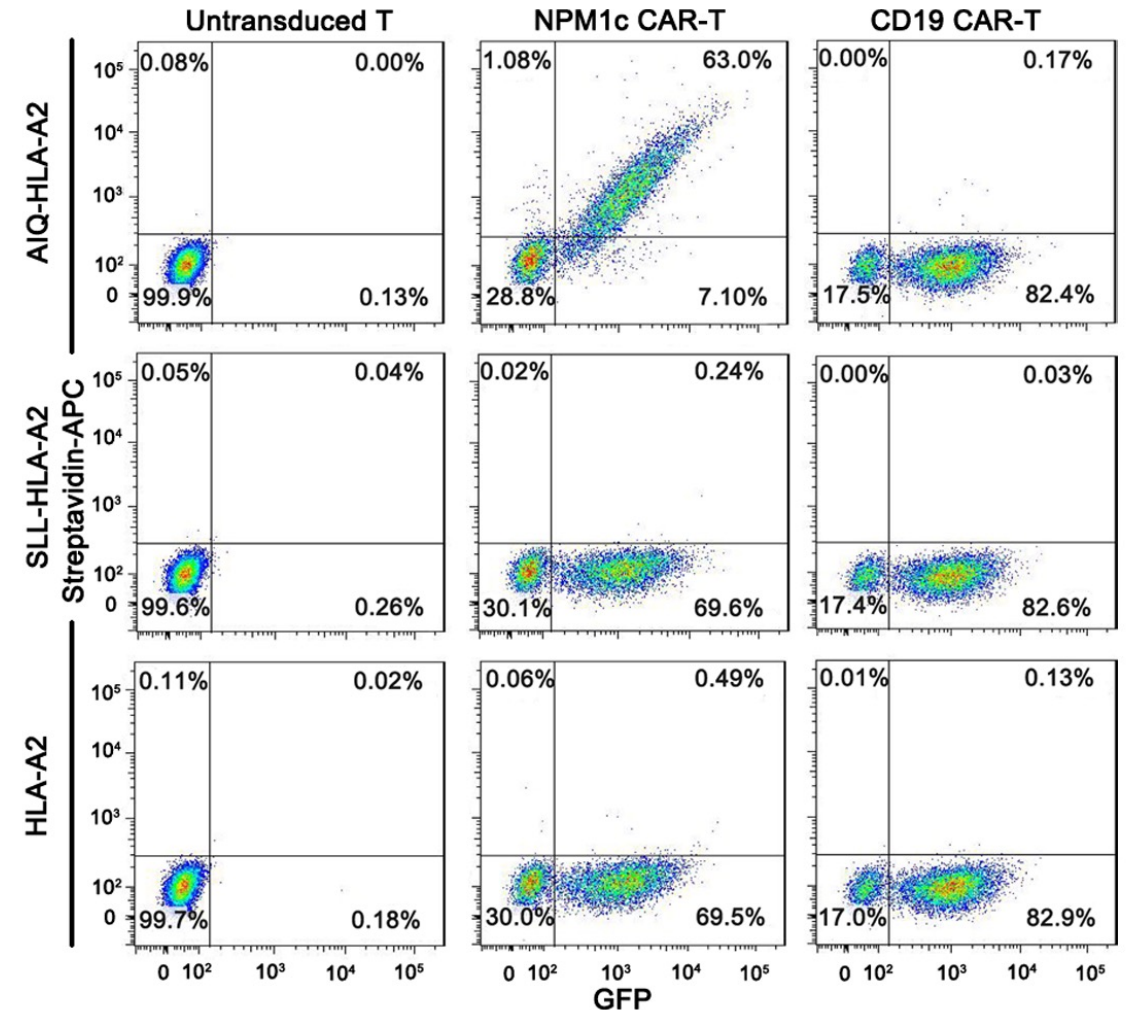
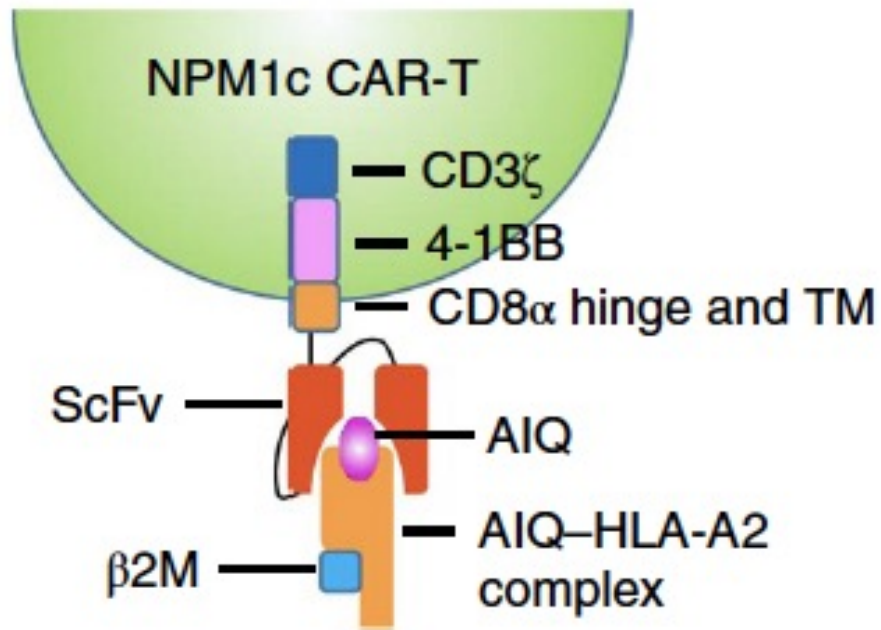


Figure 3-23 Immunobiology, 6/e. (© Garland Science 2005)

# Isolation of scFv specific for NPM1c neoepitope/HLA-A2 complex

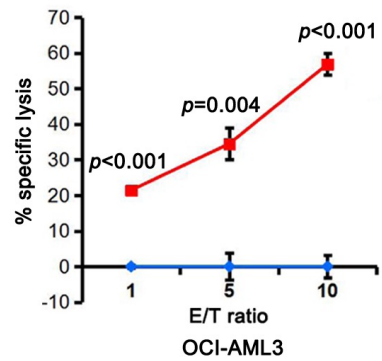


# Specific binding of neoepitope/HLA to NPM1c CAR on T cells

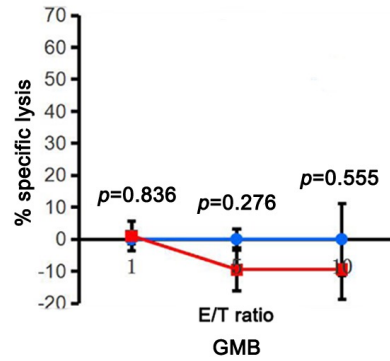


# CAR-T cells specifically kill AML with NPM1c mutation

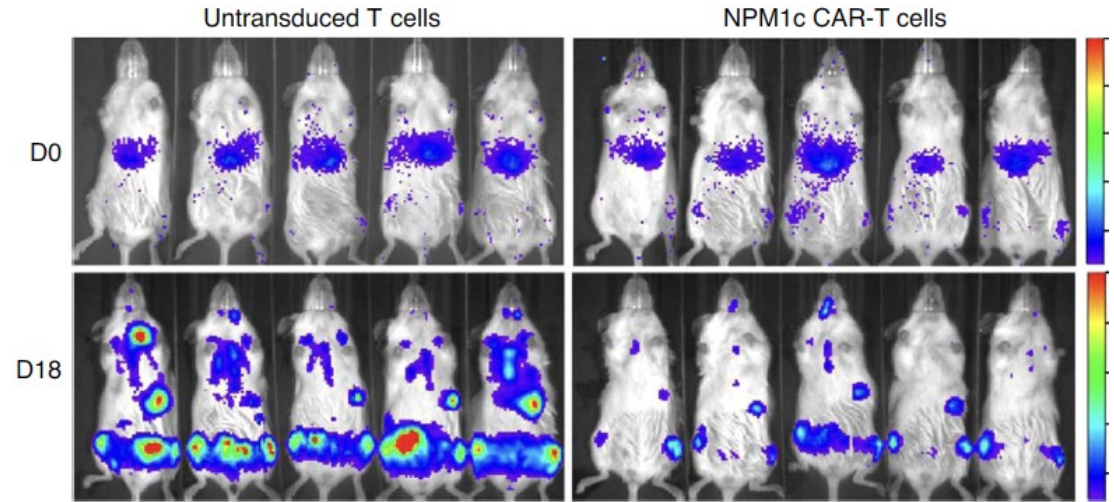
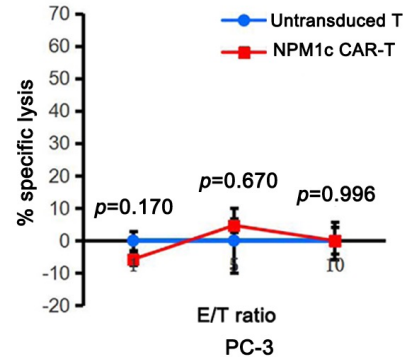
**NPM1c<sup>+</sup>, A2<sup>+</sup>**



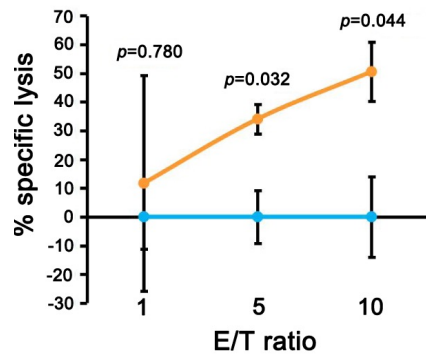
**NPM1c<sup>-</sup>, A2<sup>+</sup>**



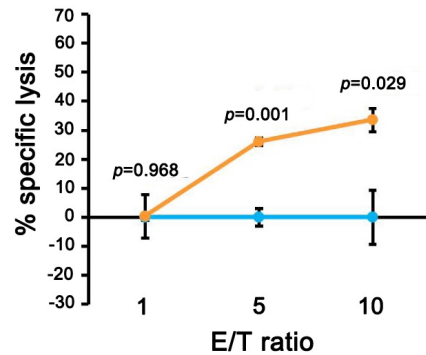
**NPM1c<sup>-</sup>, A2<sup>-</sup>**



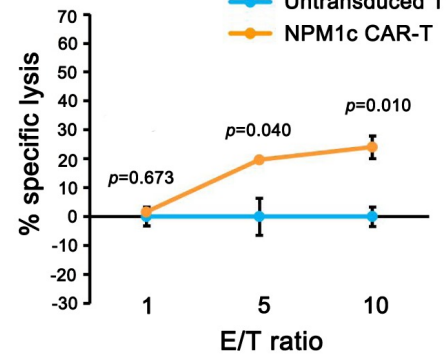
**Donor 1**



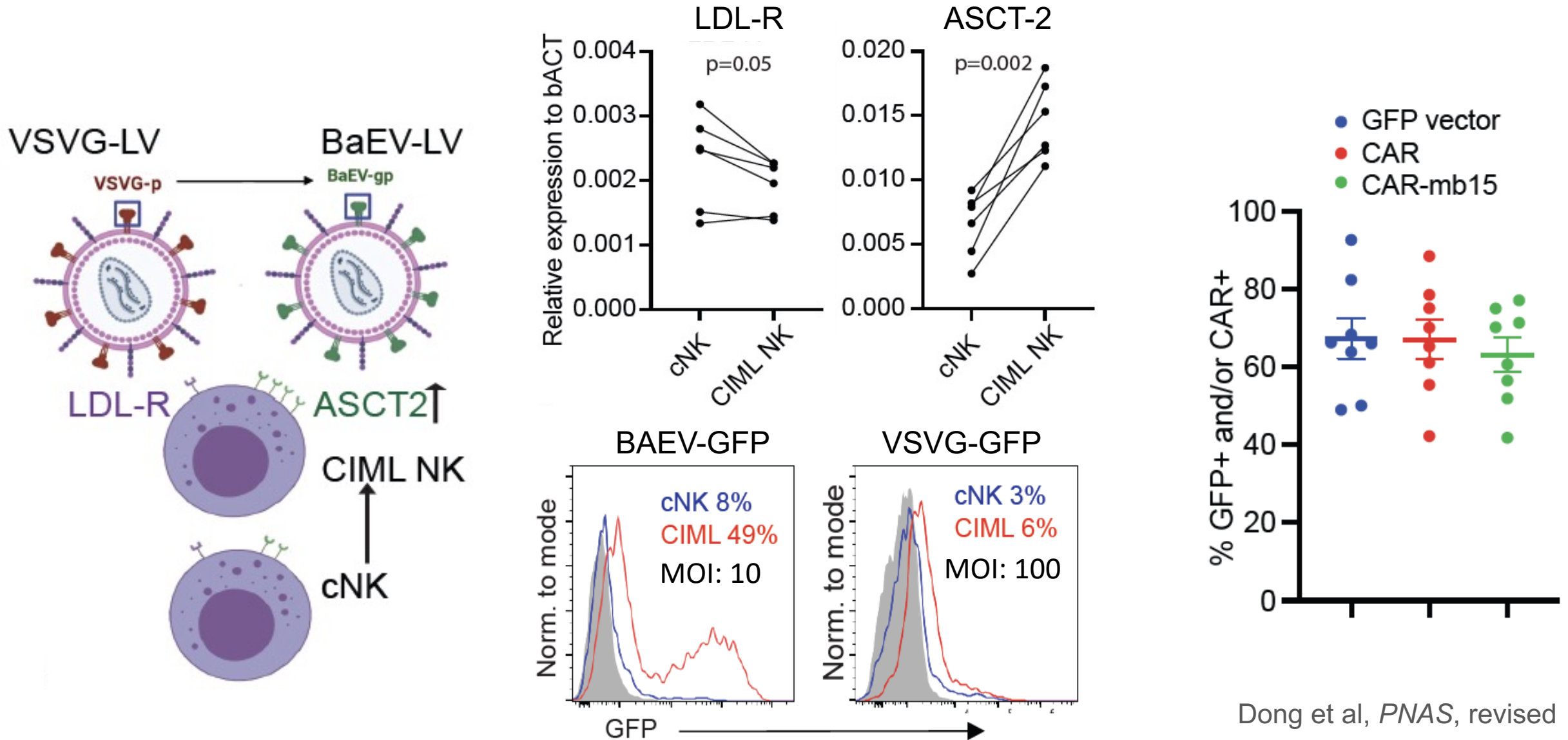
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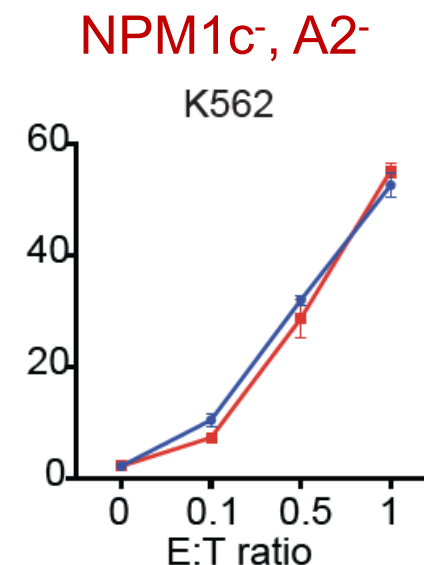
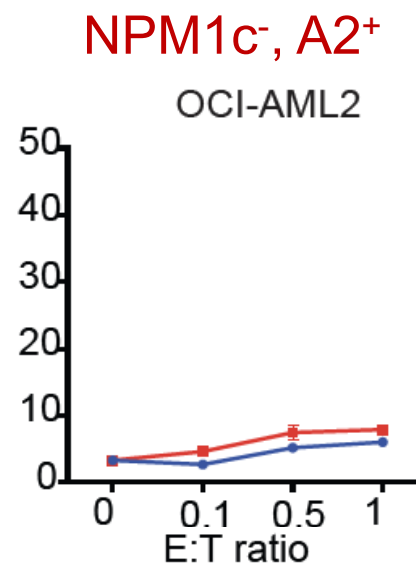
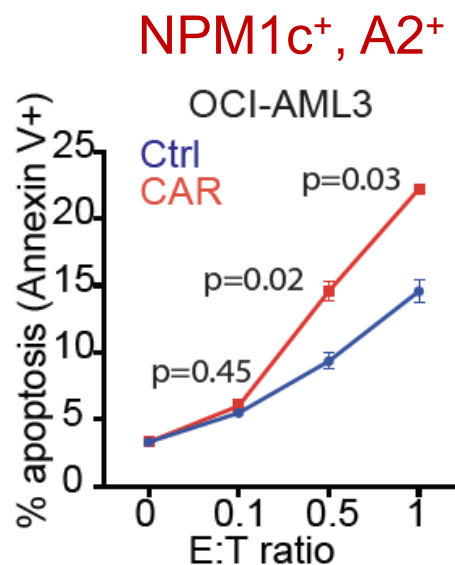
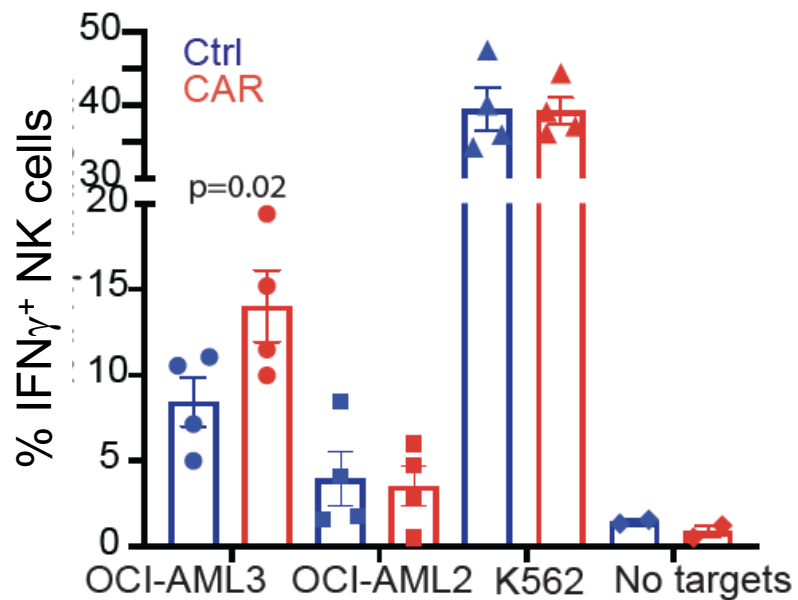
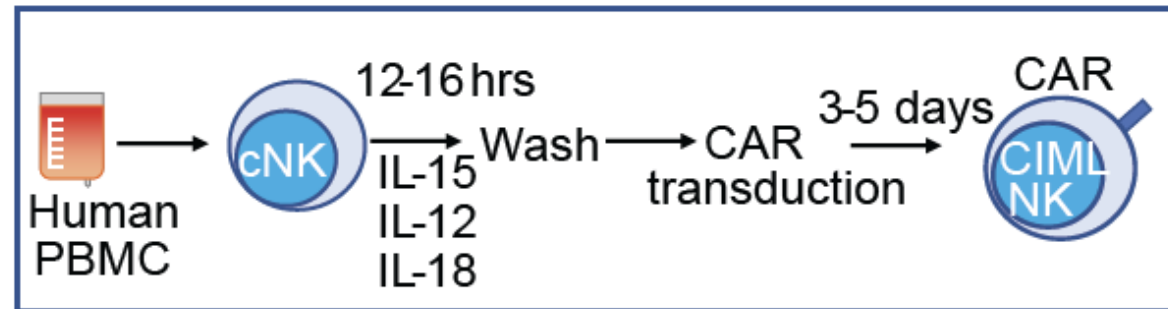
**Donor 3**



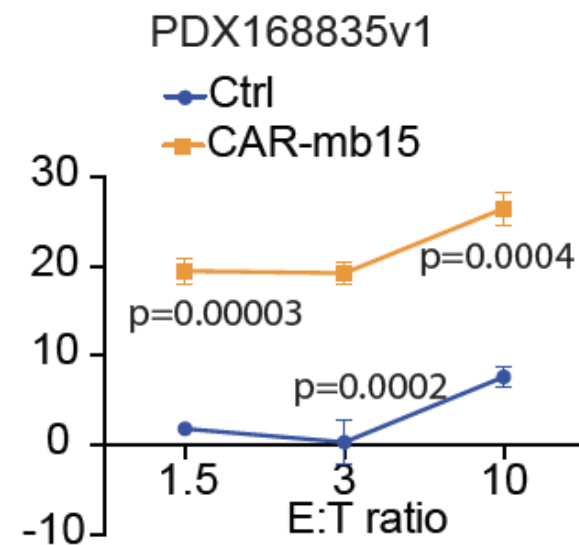
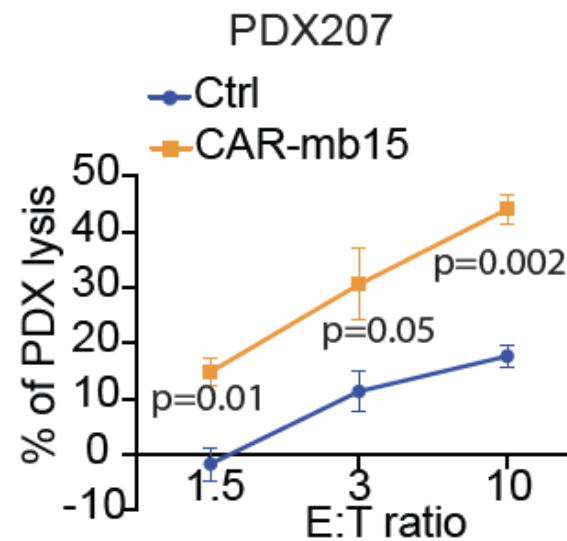
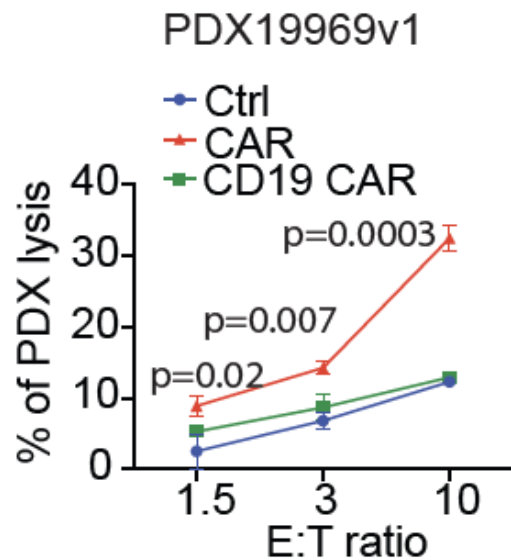
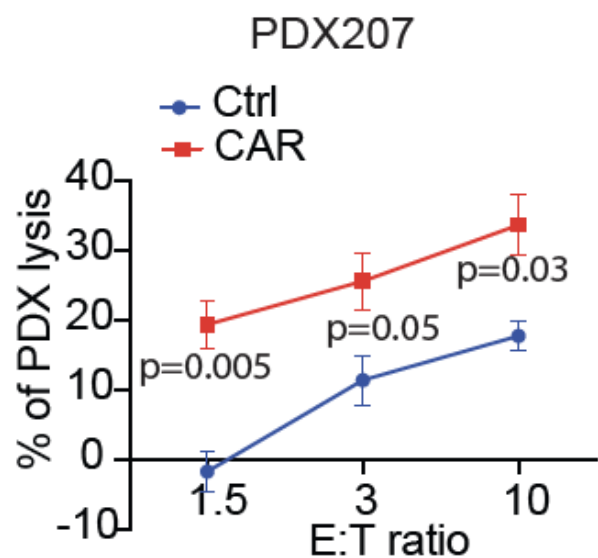
# Efficient transduction of NK cells with Baboon retroviral envelope glycoprotein pseudotyped lentivirus



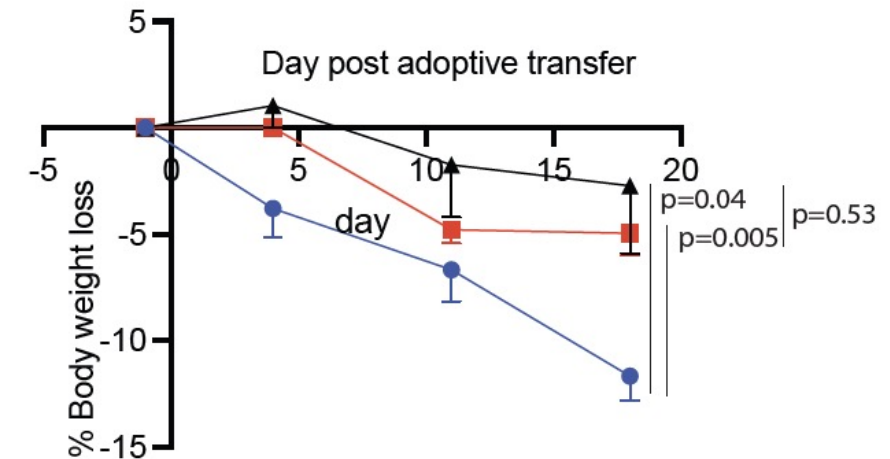
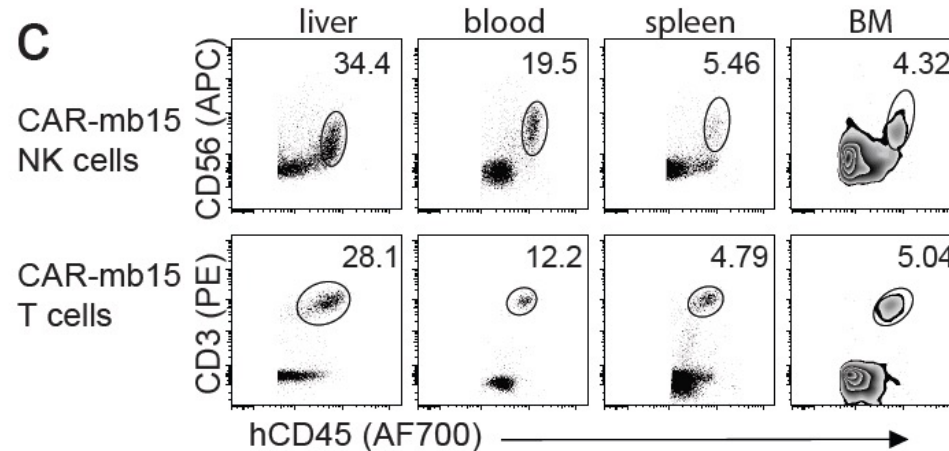
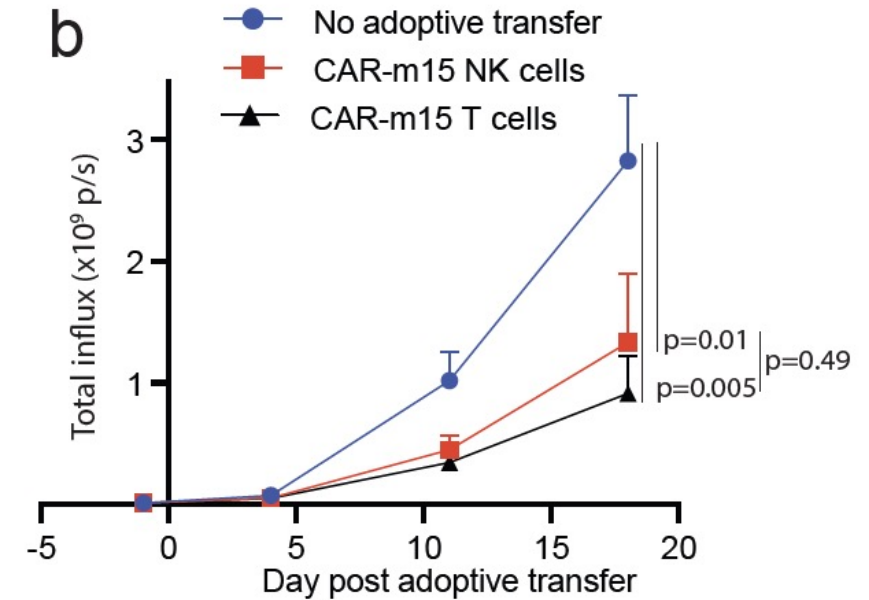
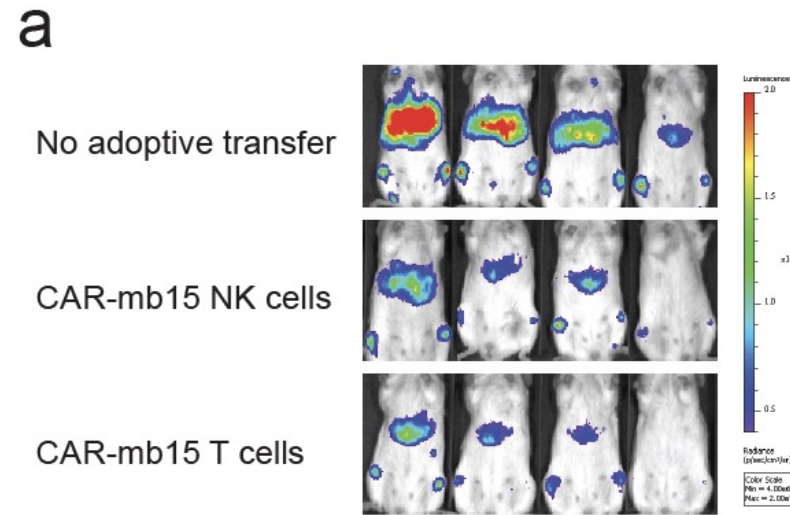
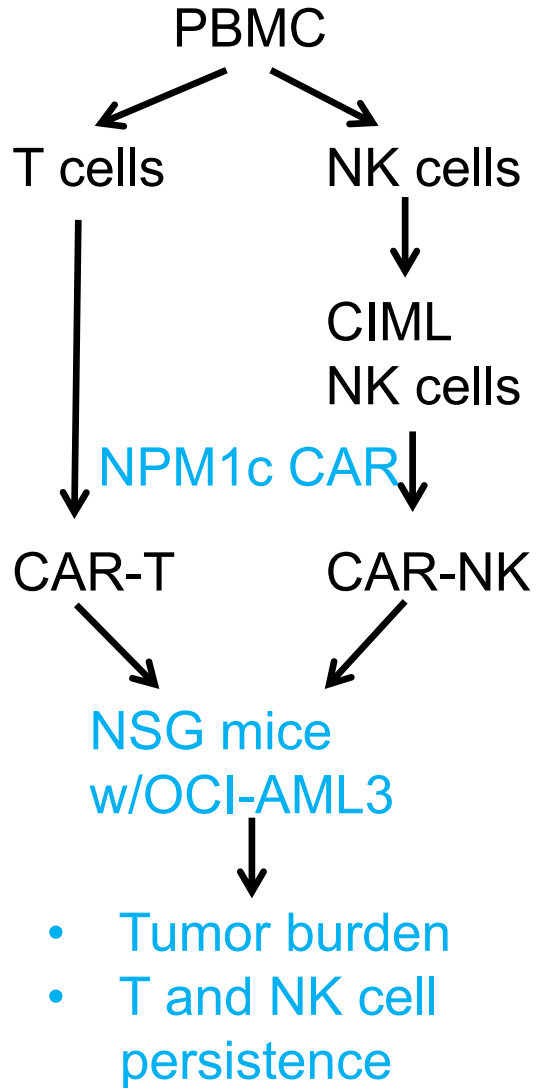
# Two modes of target cell killing by CAR-NK cells



# Two modes of target cell killing by CAR-NK cells



# Comparison of T and NK cells expressing the same CAR

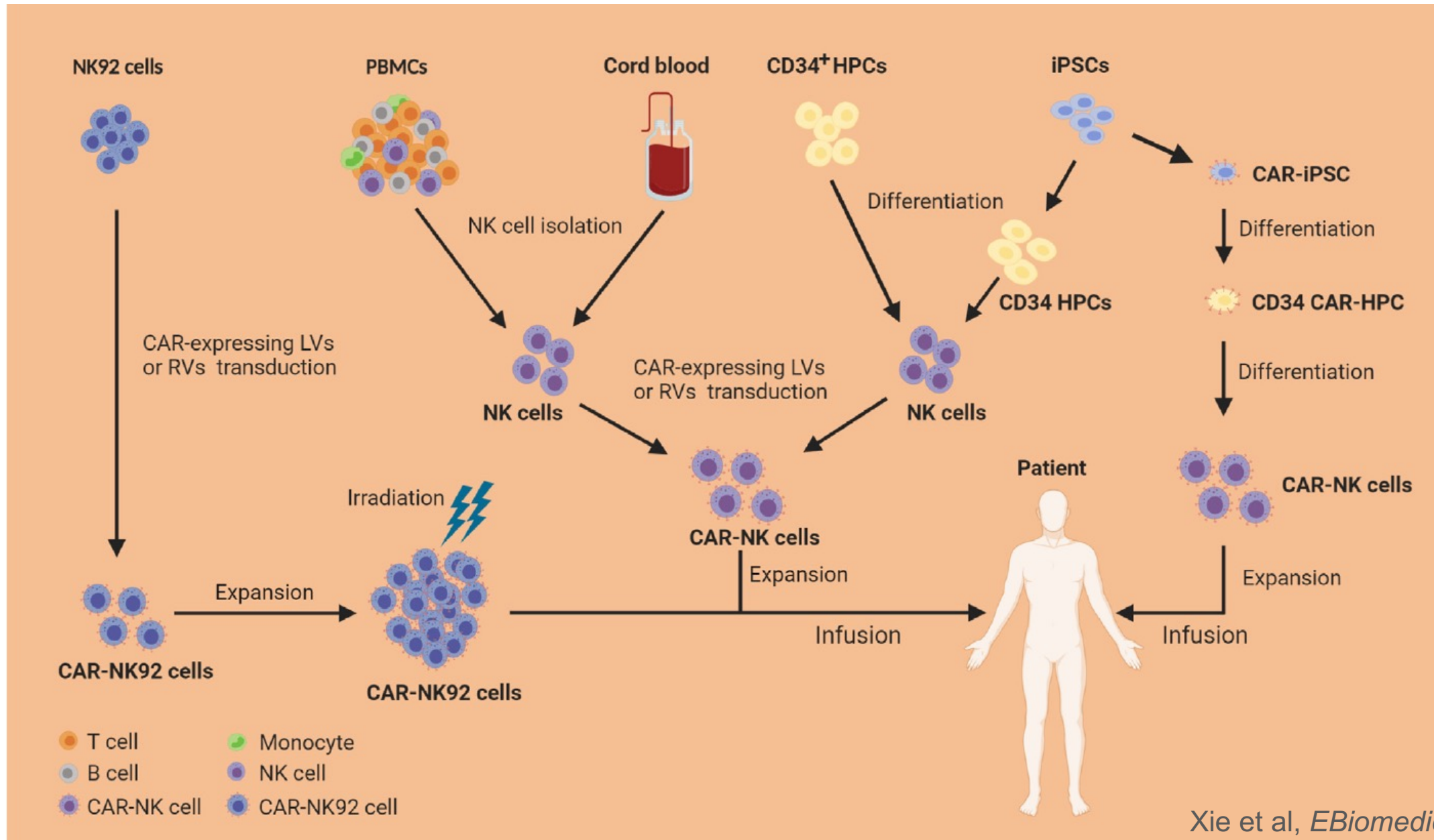




# Challenges for CAR-T and CAR-NK cell therapies

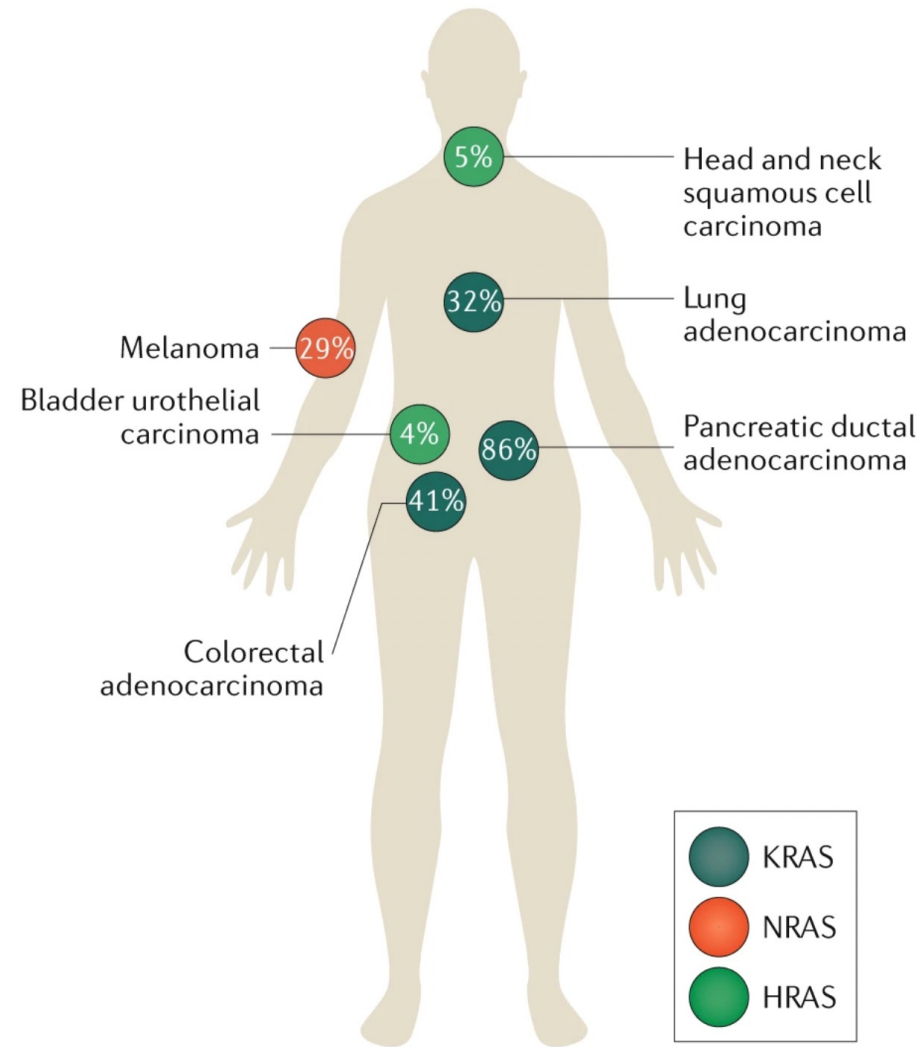
- Toxicities
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  - Cost
    - Individualized therapy
- NK cells
  - Target tumor-driver mutations
  - Memory-like NK cells
  - Induce endogenous immune responses
  - Allogeneic NK cells
  - In vivo CAR transduction

# Allogeneic and iPSC-derived NK cells



# Kras mutations and cancer

**a**



**b**

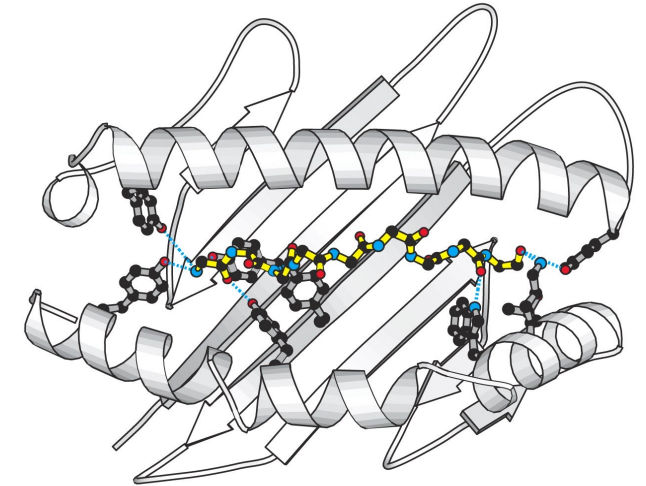
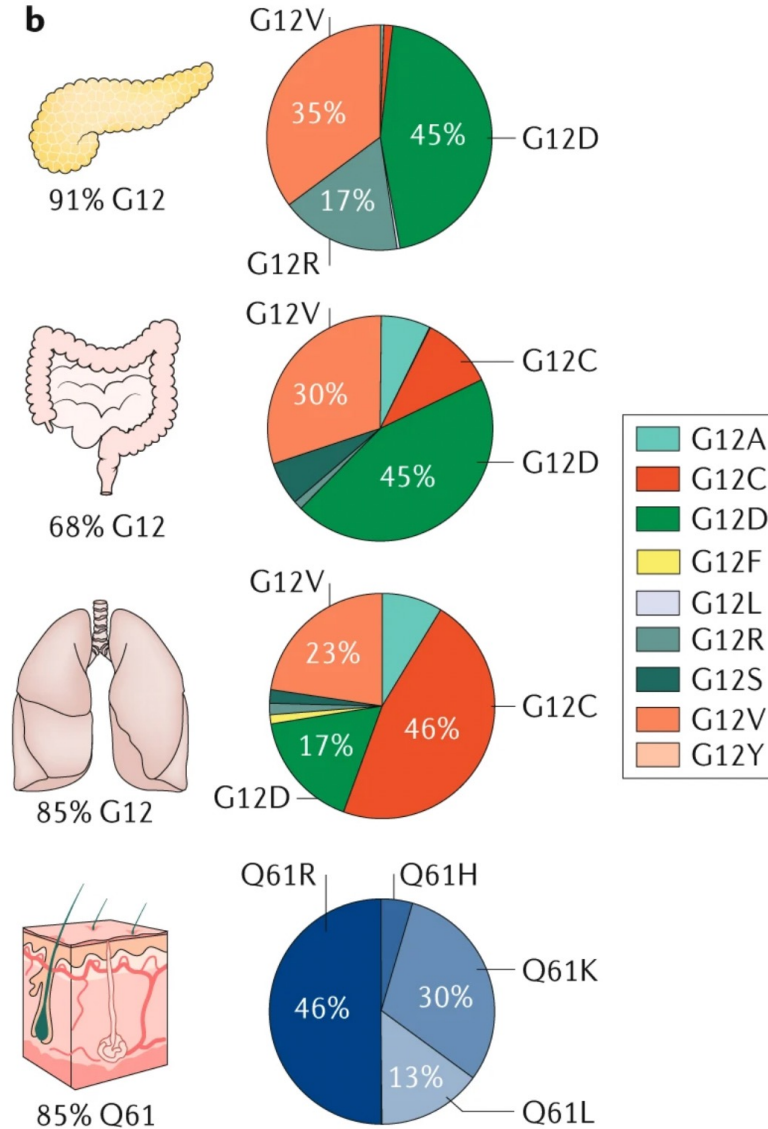
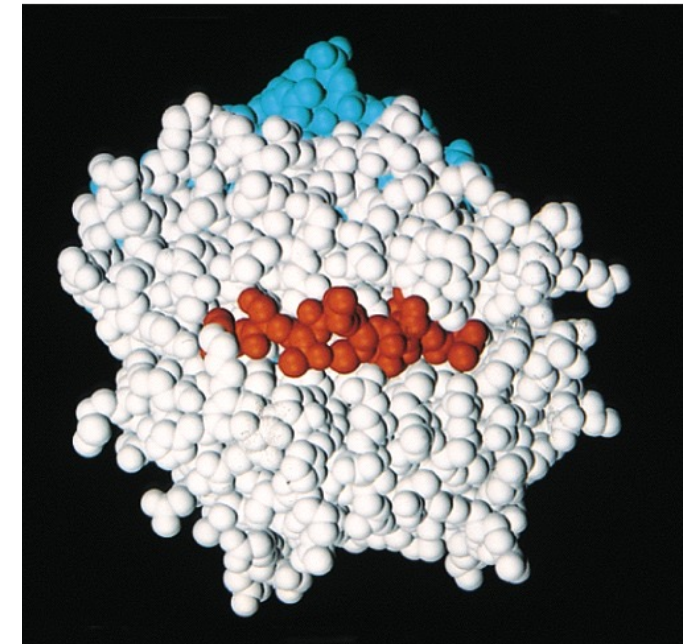


Figure 3-23 Immunobiology, 6/e. © Garland Science 2005



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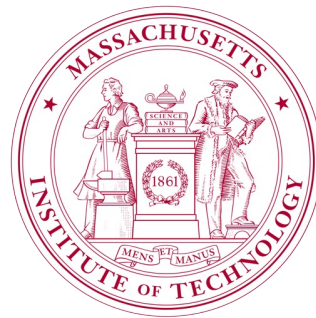
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- **Han Dong**

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