Targeting myeloid tumors by Off-the-Shelf NK cells using an NKG2C-IL15-CD33 Trispecific Killer Engager

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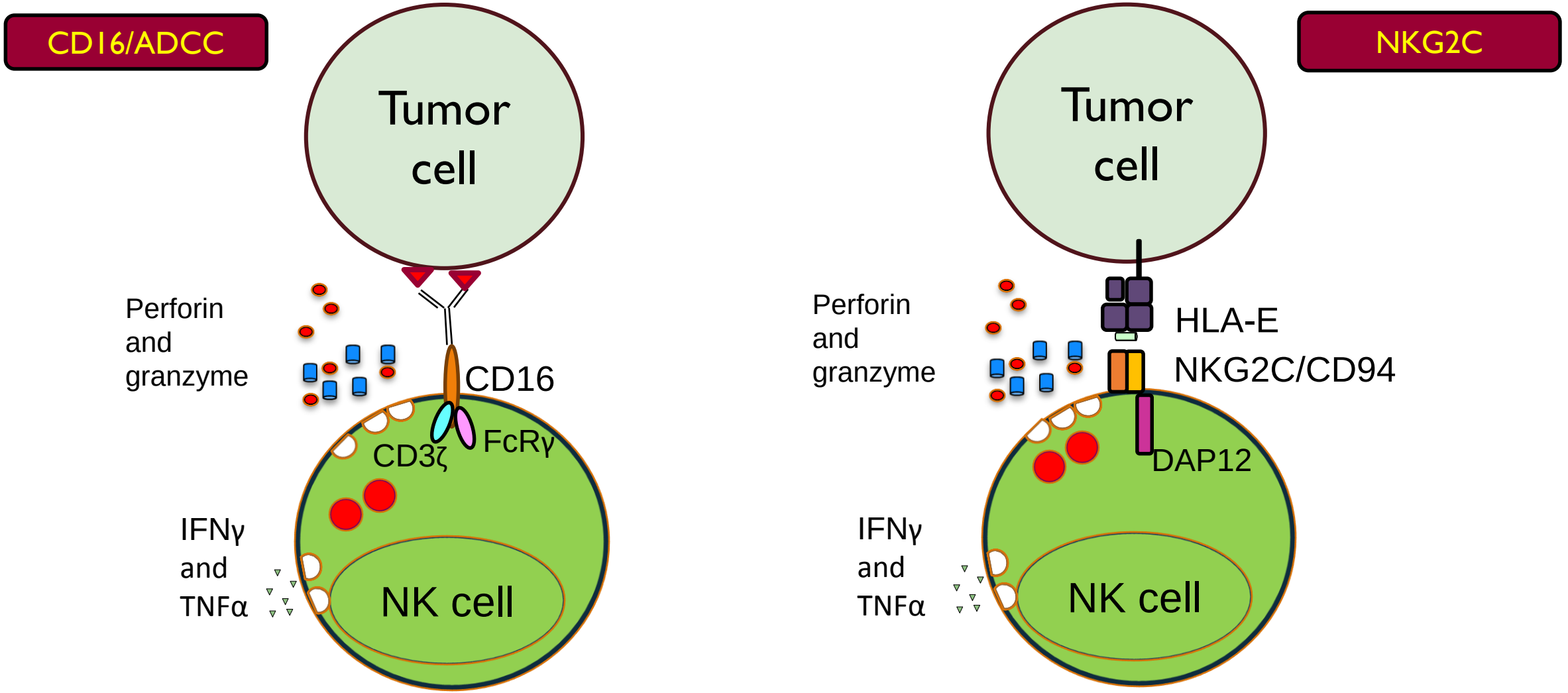
NK Cell Immunotherapy

- Natural killer cells recognize tumors and virally infected cells
- They mediate cytotoxicity and produce cytokines
- Lymphodepleting chemotherapy and haploidentical NK cell adoptive transfer have been used successfully to treat patients with refractory AML with CR rates of 30-50%
- New strategies are needed to
  - Further improve the rate and duration of CR
  - Enhance NK cell activity and persistence
  - Promote antigen specificity

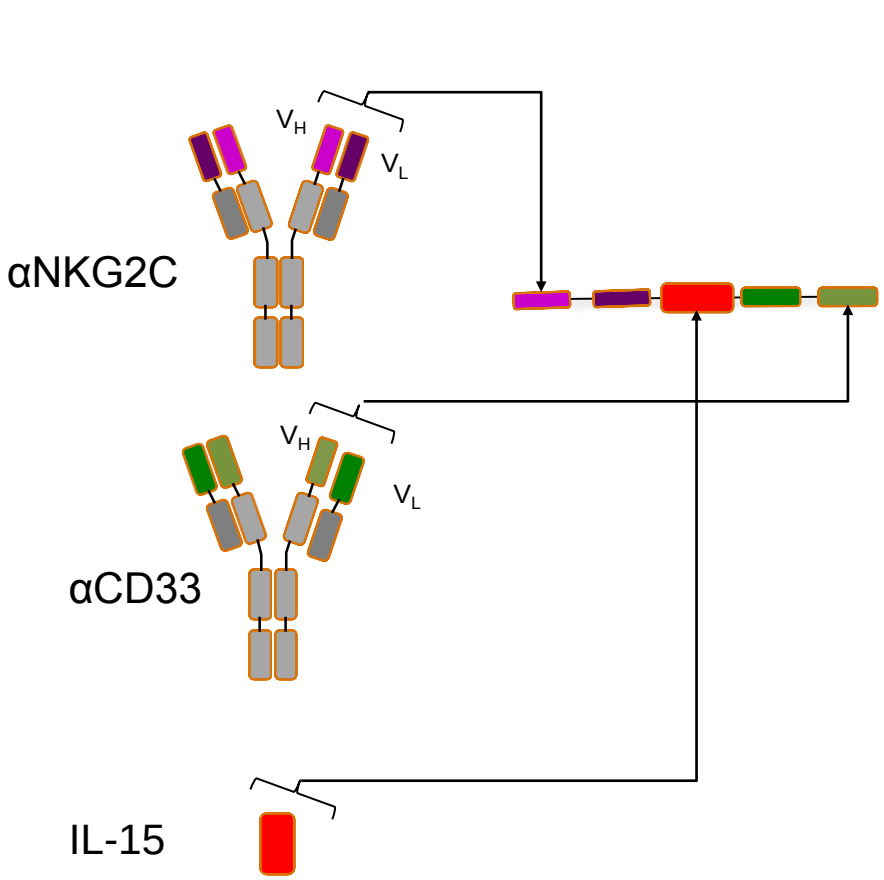
Adaptive NK cells

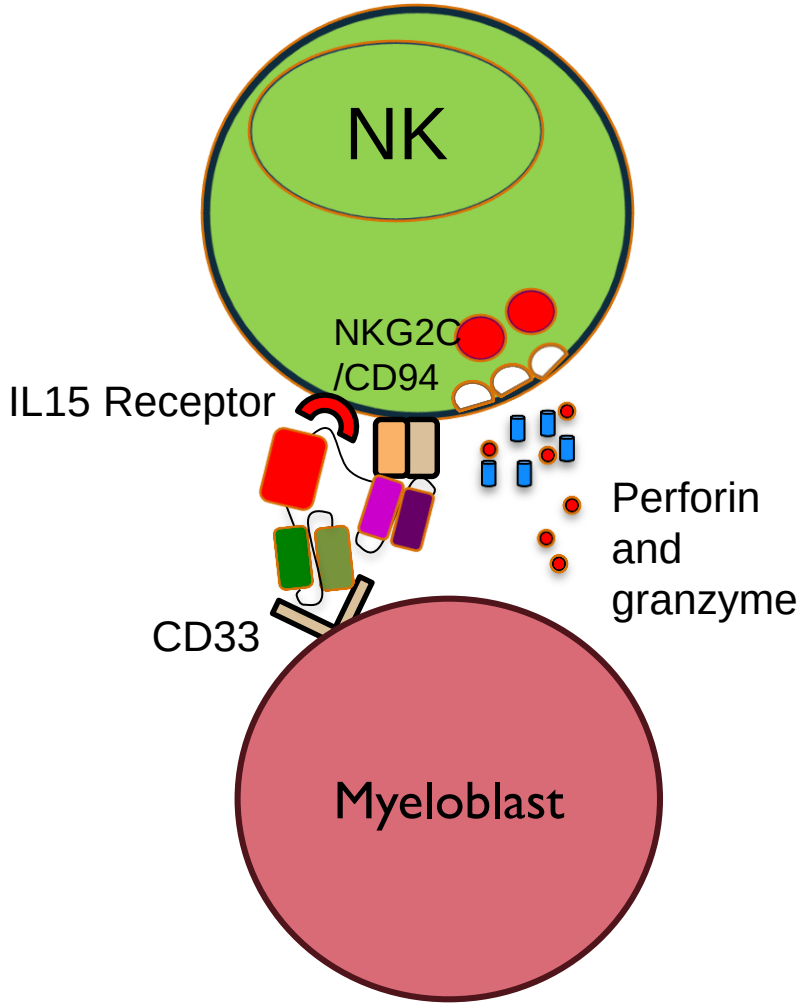
- Induced by CMV exposure
  - Long lived NKG2C+ cells with properties of immune memory
  - Methylation pattern of CD8+ T cells
- CMV reactivated recipients after reduced intensity conditioning allo-BMT have high abundance of adaptive NK cells
  - Correlated to relapse protection
- Decrease surface checkpoints
- Resist cellular suppression by MDSC and T-regs
- Exhibit enhanced antibody dependent cell mediated cytotoxicity (ADCC)

NK cells can mediate anti-tumor efficacy through their Fc receptor (CD16) and NKG2C

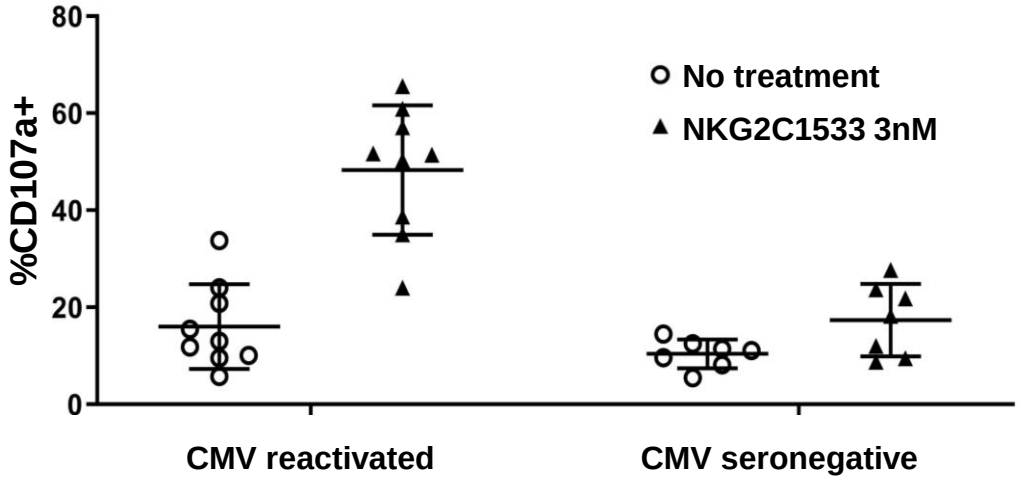


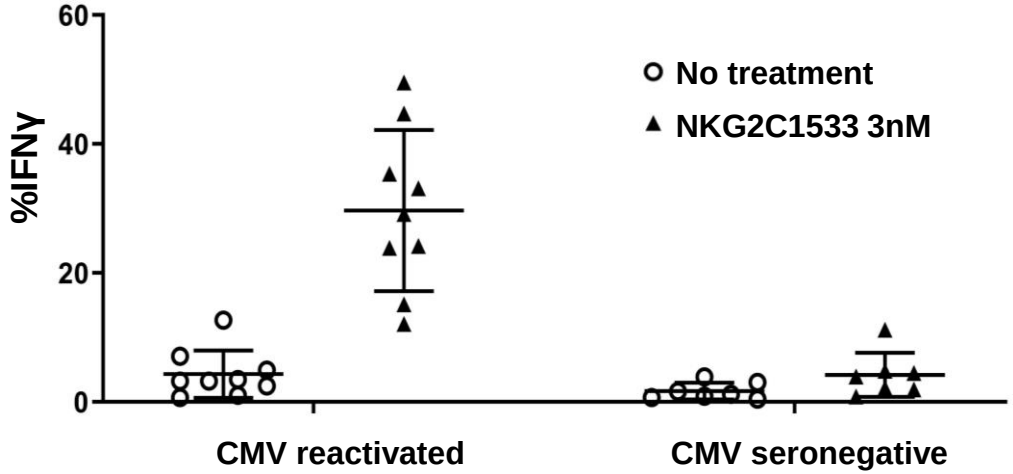
Trispecific Killer Engager to manipulate the immune system

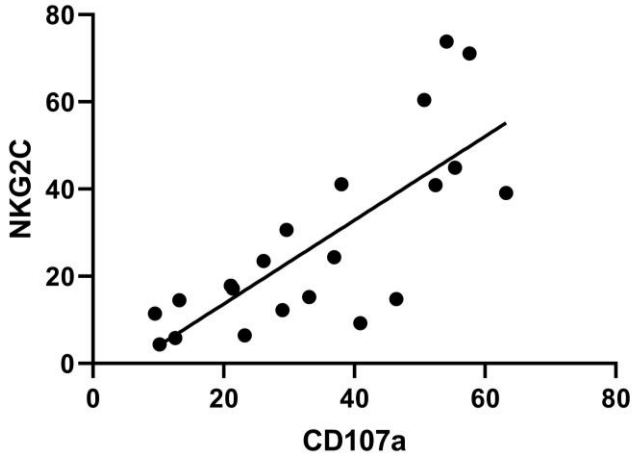




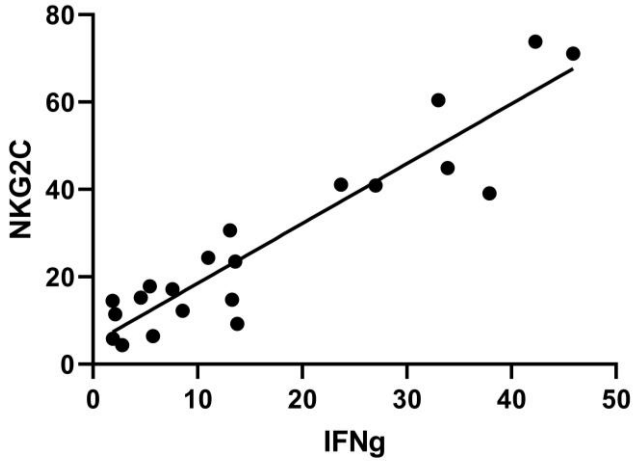
NKG2C1533 TriKE activation against THP1 AML cell line after transplant is dependent on the frequency of NKG2C+ adaptive NK cells





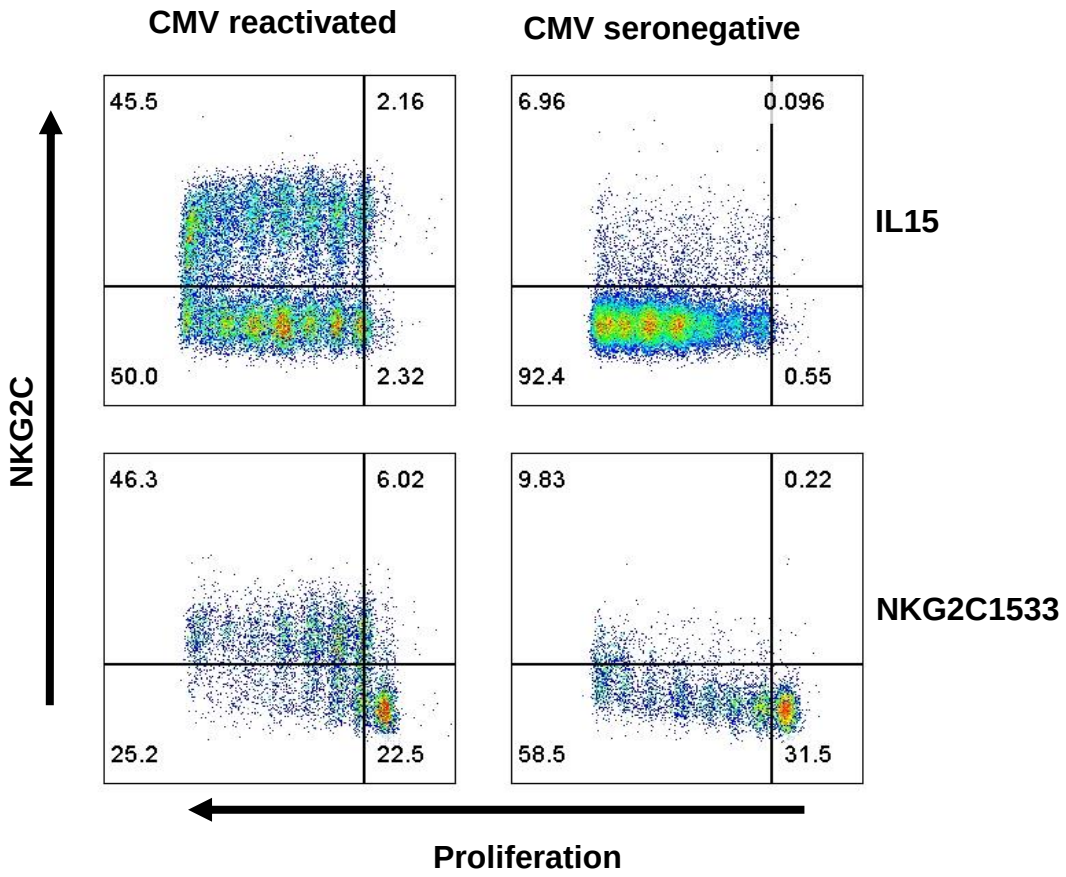


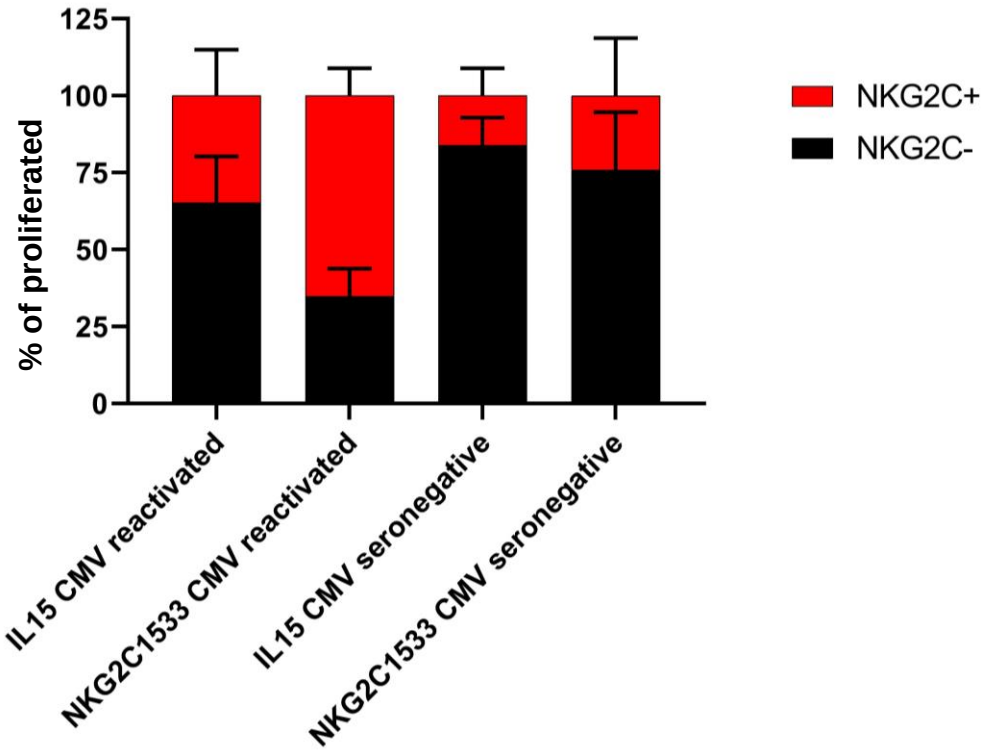
R^2: 0.5918
P value : <0.0001



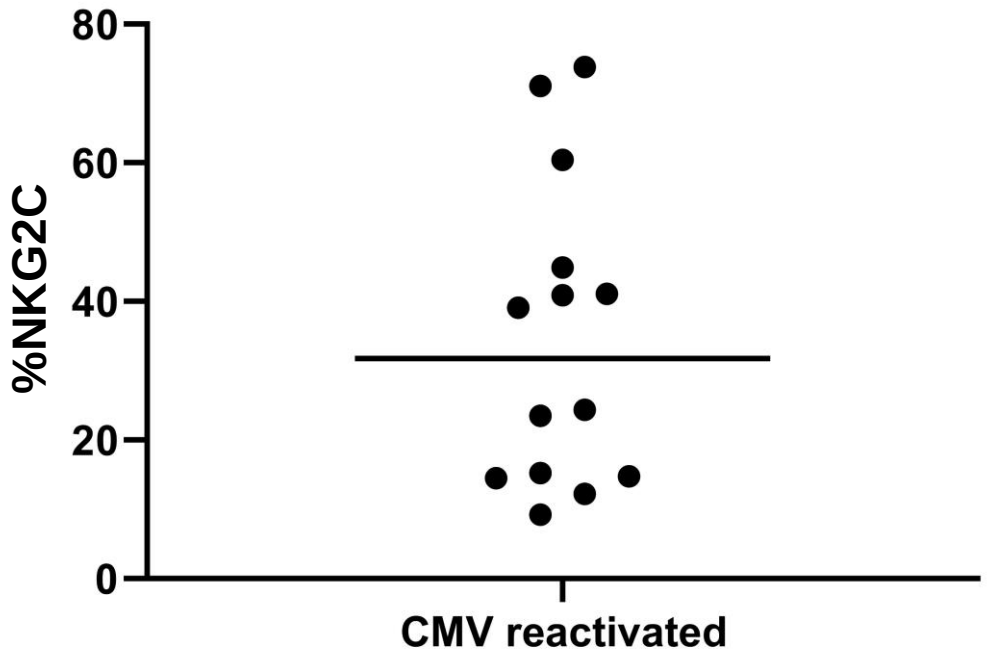
R^2: 0.8697
P value : <0.0001

NKG2C1533 TriKE preferentially proliferates NKG2C+ adaptive NK cells

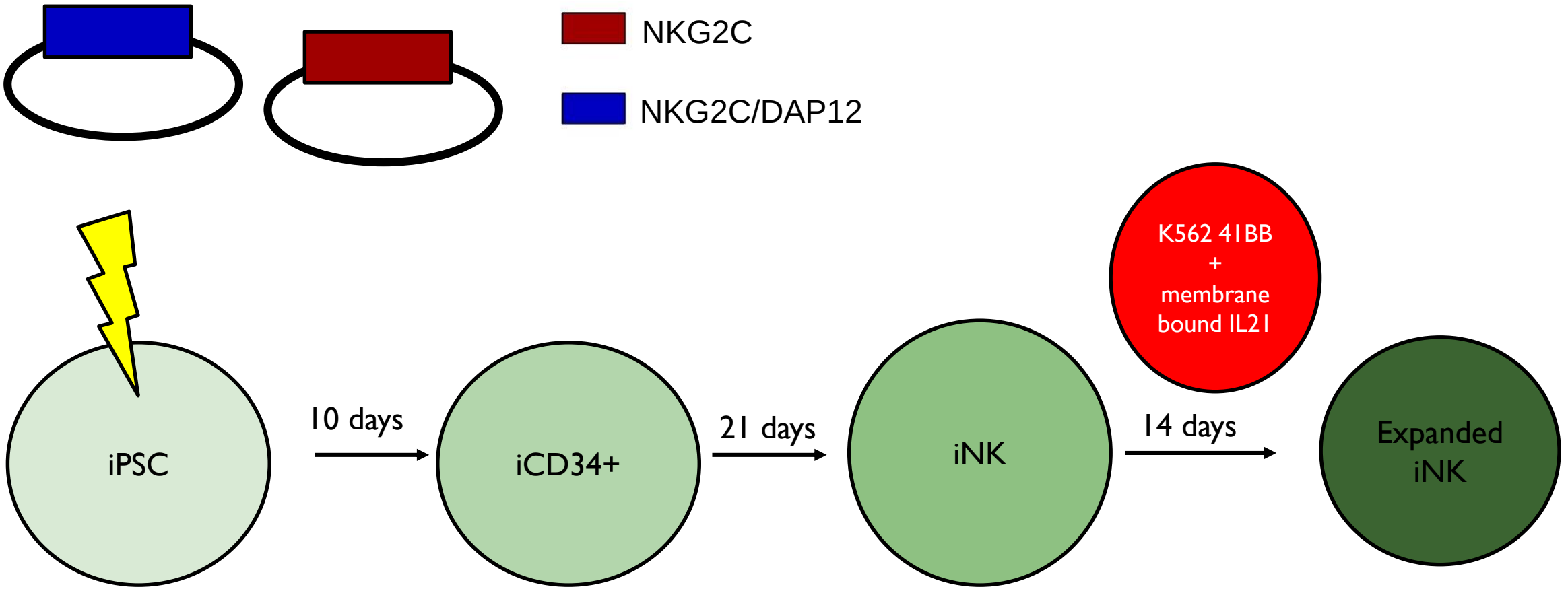




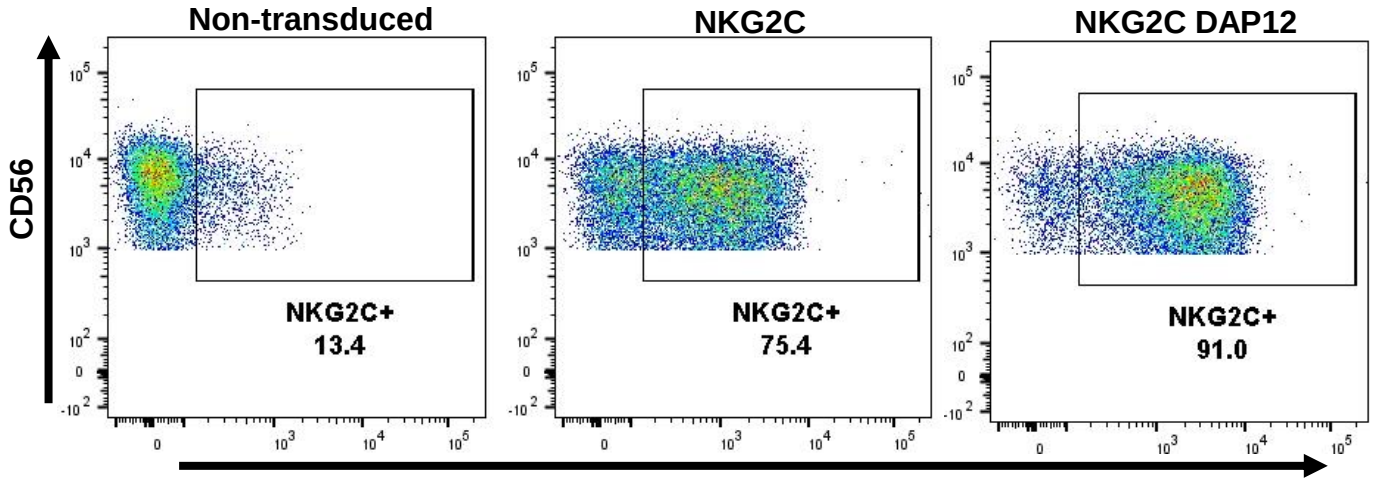
Even in CMV reactivated patients, NKG2C+ NK cells is variable

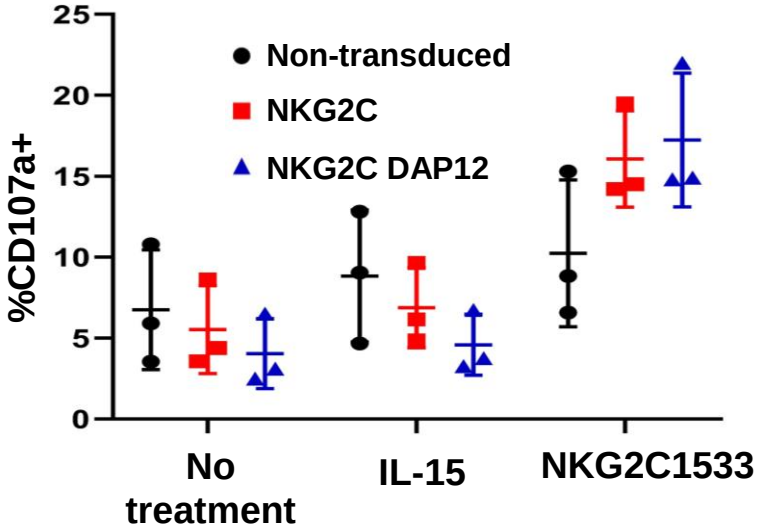


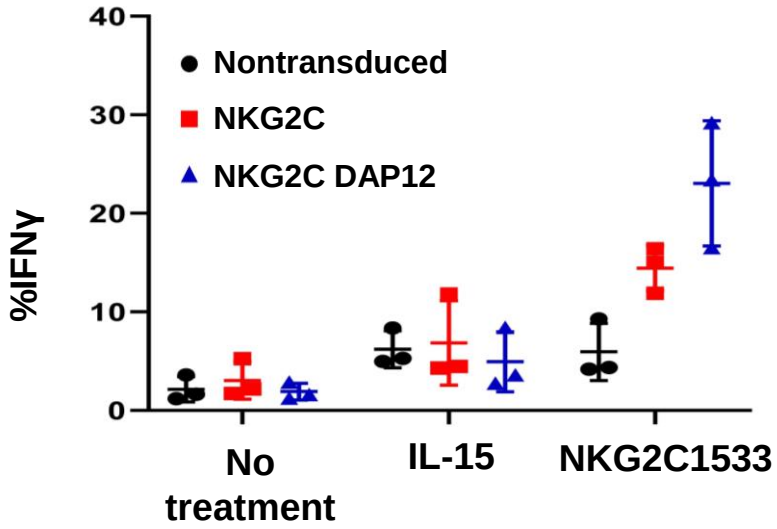
Induced Pluripotent stem cells as a more consistent source for NKG2C+ cells for adoptive transfer



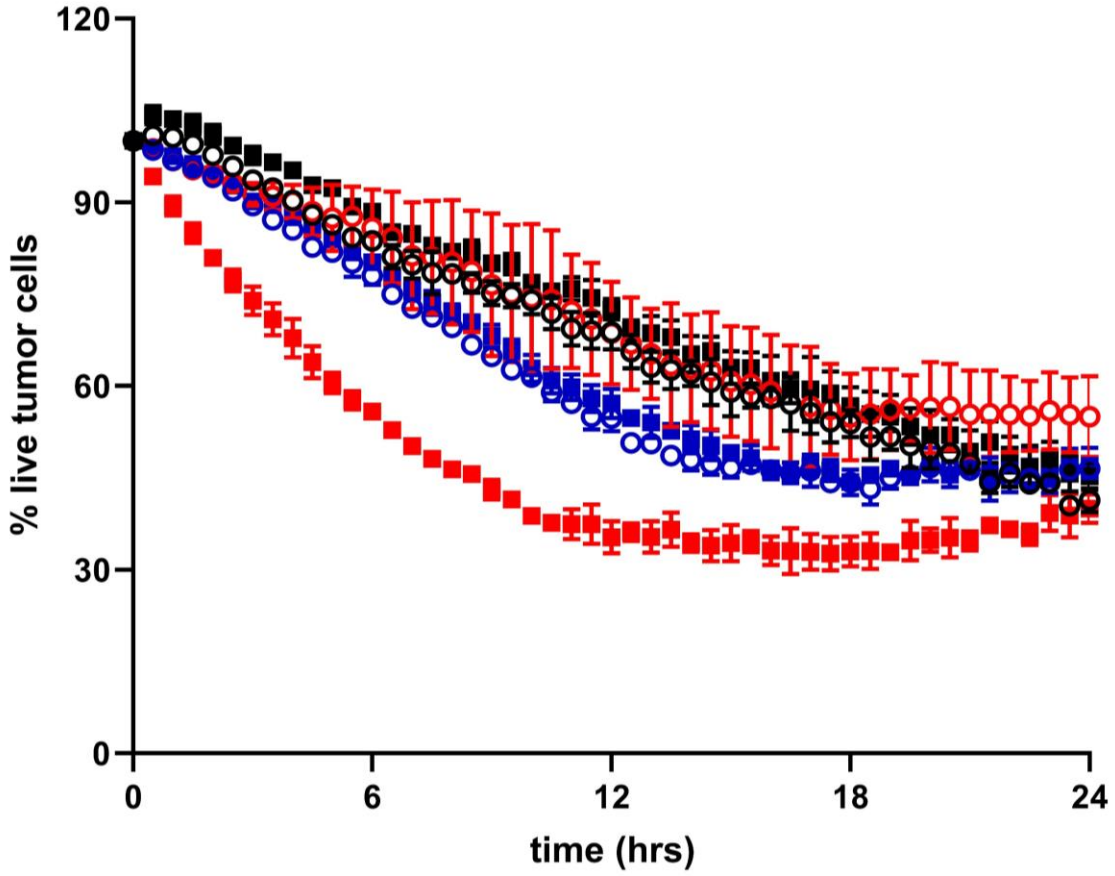
NKG2C1533 TriKE induces best overall function in NKG2C/DAP12 iPSC derived iNK cells against THP1







NKG2C1533 TriKE promotes NKG2C/DAP12 transduced iNK to kill THP1 AML targets



No treatment
IL15
NKG2C1533
Non-transduced

No treatment
IL15
NKG2C1533
NKG2C DAP12

Conclusions

- NKG2C1533 TriKE preferentially activates and proliferates NKG2C^{+} adaptive NK cells.
- NKG2C1533 TriKE can be used in post transplant patients with high NKG2C^{+} cells.
- NKG2C1533 TriKE is more specific to NK cells compared to CD16 targeting agents that may bind to neutrophils.
- iNK engineered to express NKG2C with its adaptor DAP12 have enhanced function in combination with NKG2C1533 TriKE.
- Xenogeneic experiments testing NKG2C/DAP12 iNK and NKG2C1533 TriKE against established myeloid tumors are ongoing.

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