Harnessing Adaptive NK Cells in Cancer Immunotherapy

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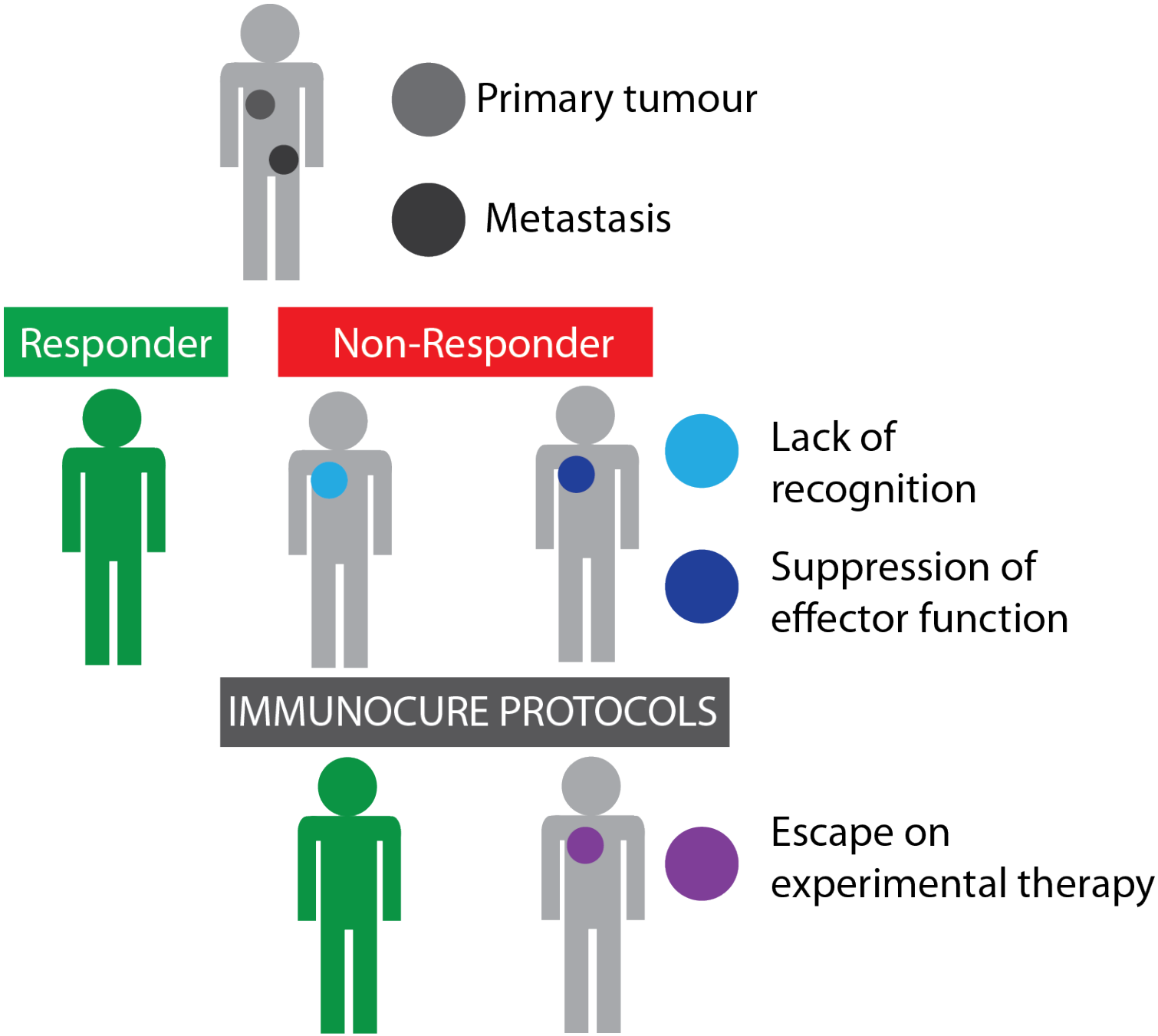
“Immunotherapy against cancer is like drying an ocean with an hairdryer”

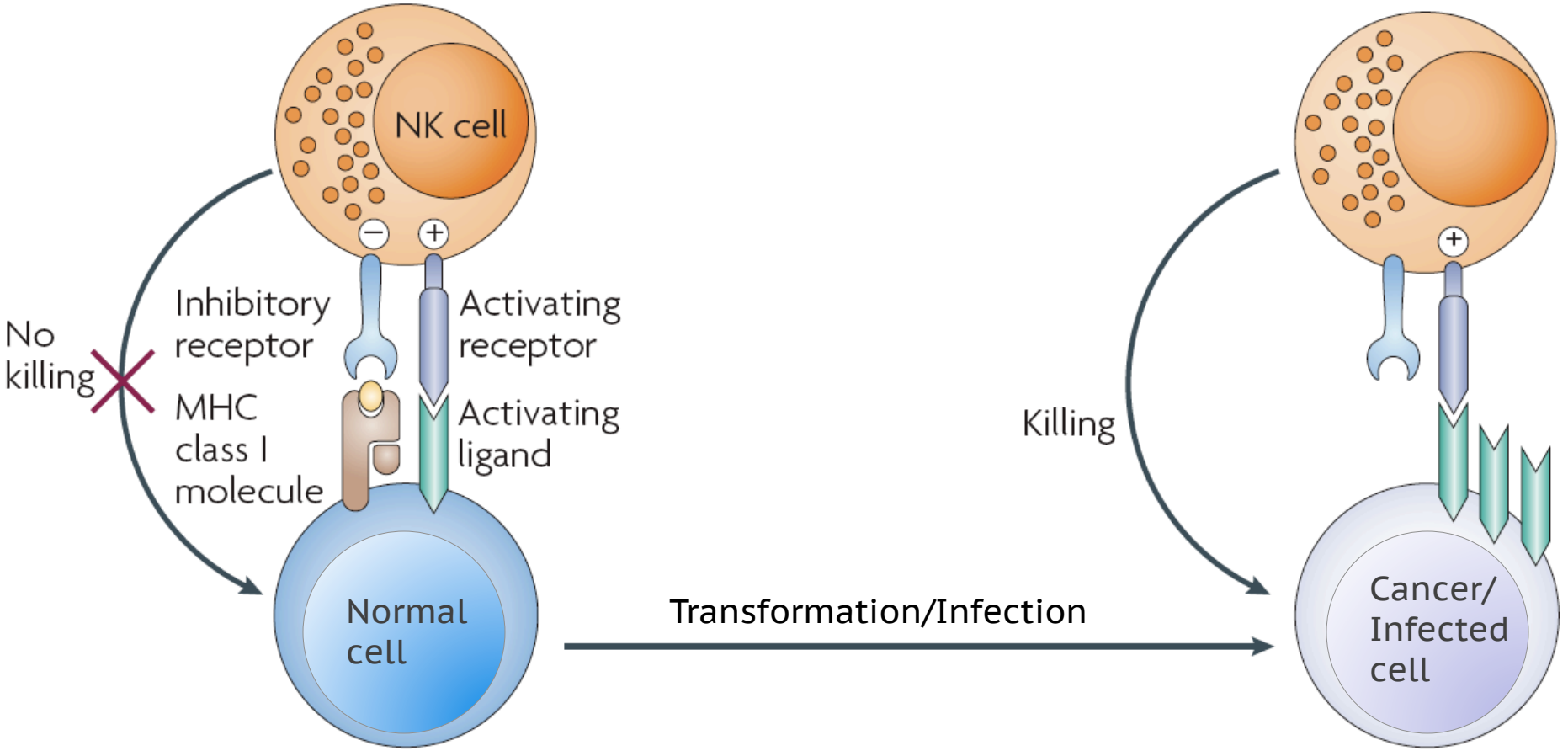
Challenge

To decipher the cellular and molecular mechanisms underlying immune failure and exploit this knowledge to convert clinical non-responders to responders

KG JEBSEN CENTER
for Cancer Immunotherapy

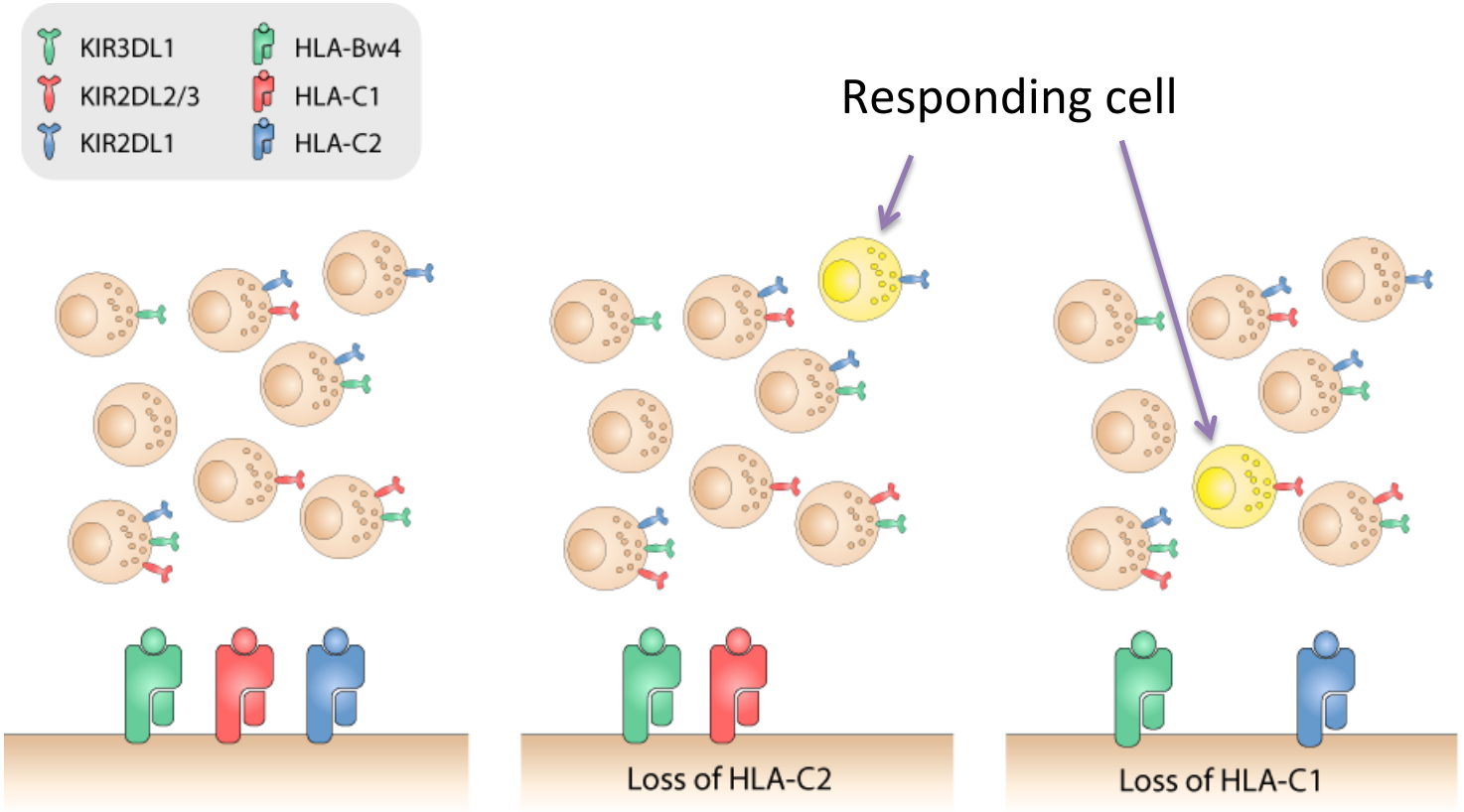

Primary tumour
Metastasis
Responder
Non-Responder
Lack of recognition
Suppression of effector function
IMMUNOCURE PROTOCOLS
Escape on experimental therapy

Regulation of NK cell function by killer cell immunoglobulin-like receptors (KIR)



Malmberg and Ljunggren, Nature Reviews Immunology 2007

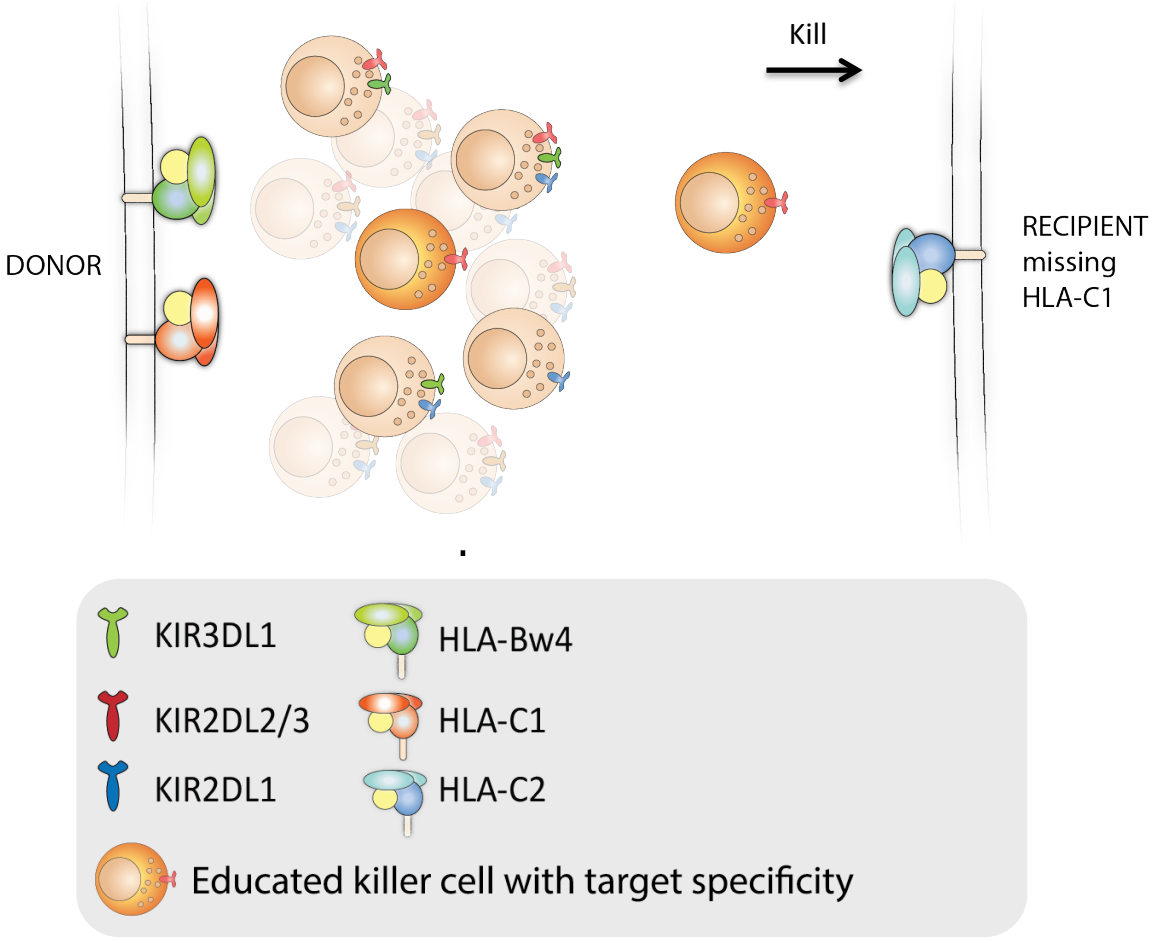
Variegated KIR expression confer tolerance and broad specificities in missing-self recognition



Haploidentical NK cell therapy -

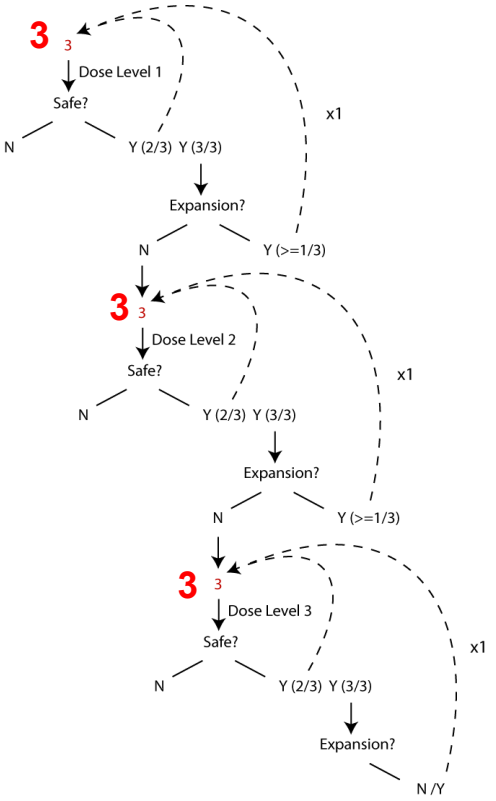
Preliminary results from a Phase I/II trial at the Karolinska Institute

NK cell therapy across HLA barriers – missing self in the new host!



Protocol Design – Refractory AML or MDS

Escalating dose of total lymphoid irradiation (TLI) and addition of Cyclosporine A



Infusion of over night
IL-2 activated
Haploidentical NK cells

-7 -6 -5 -4 -3 -2 -1 0 +1 +2 +3 +4 +5 +6 +7 +8 +9 +10 +11 +12 +13 +14 90

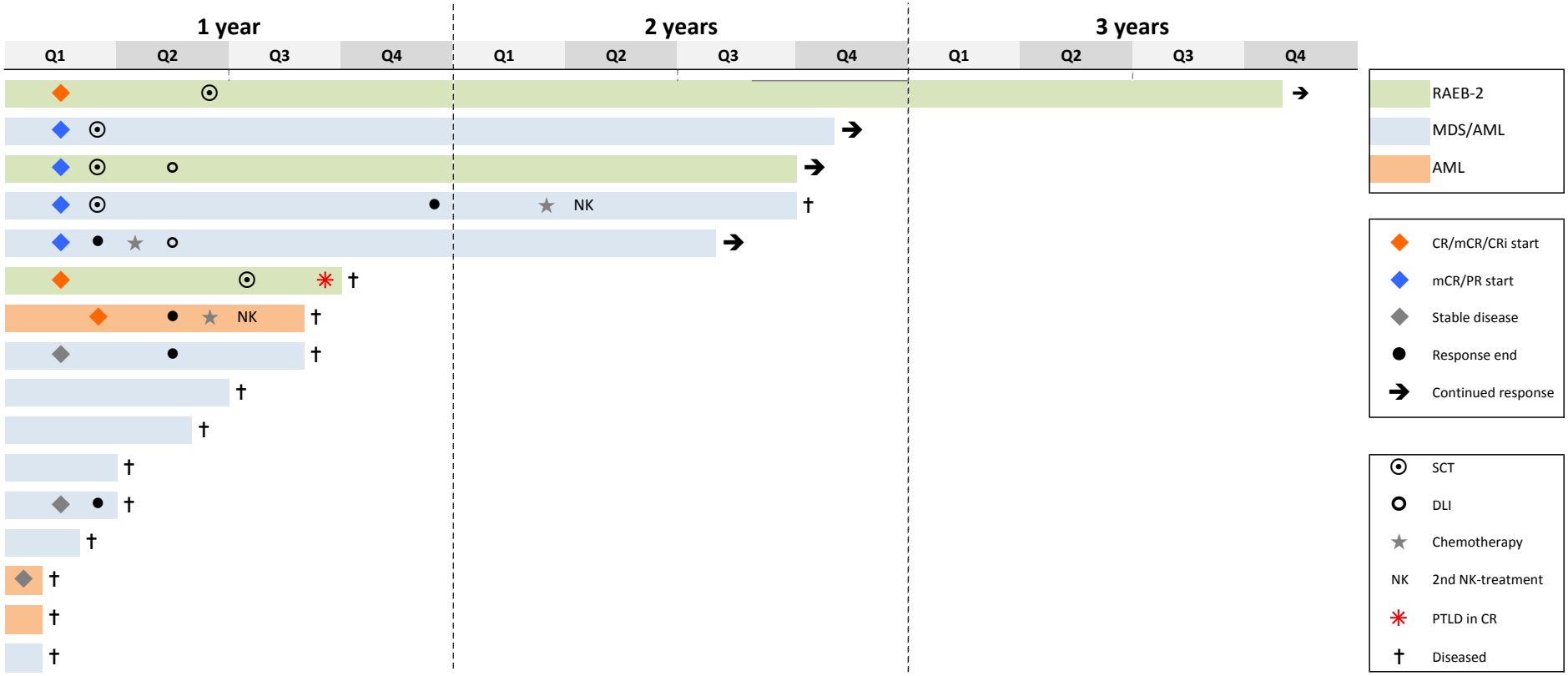
Fludarabine 25mg/m2 (Day -7 to -4)

Cyclophosphamide 25mg/kg (Day -3 to -2)

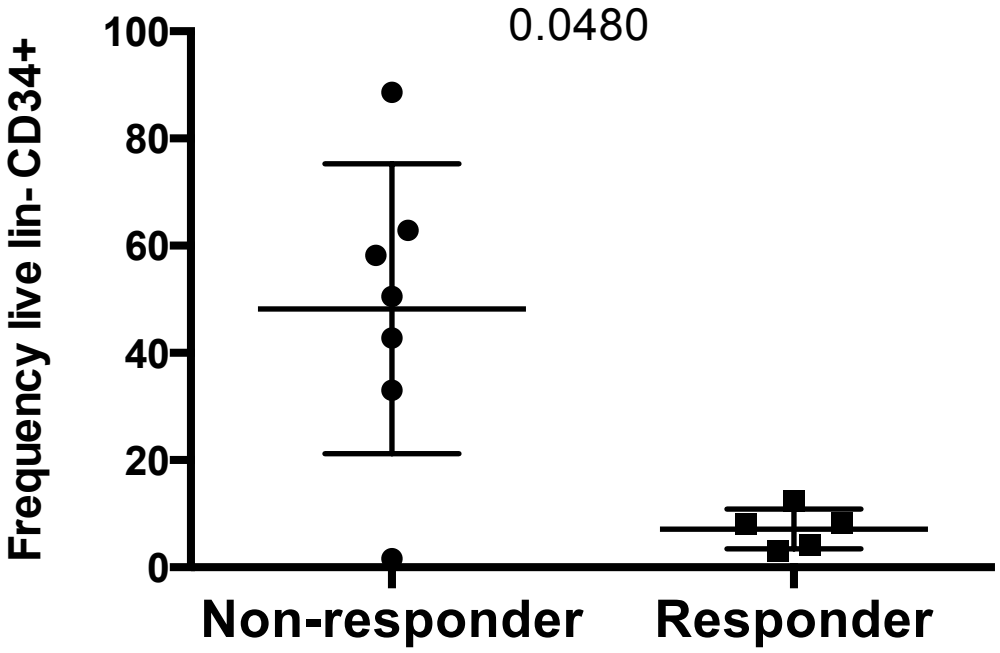
TLI 2-4 Gy (Dose Level 1 and 2) (Day -1)

Cyclosporin A (Dose Level 3) Target conc 75ng/ml (Day 0 until end of study 3 months)

6/16 patients reaching CR or PR becoming eligible for stem cell transplantation

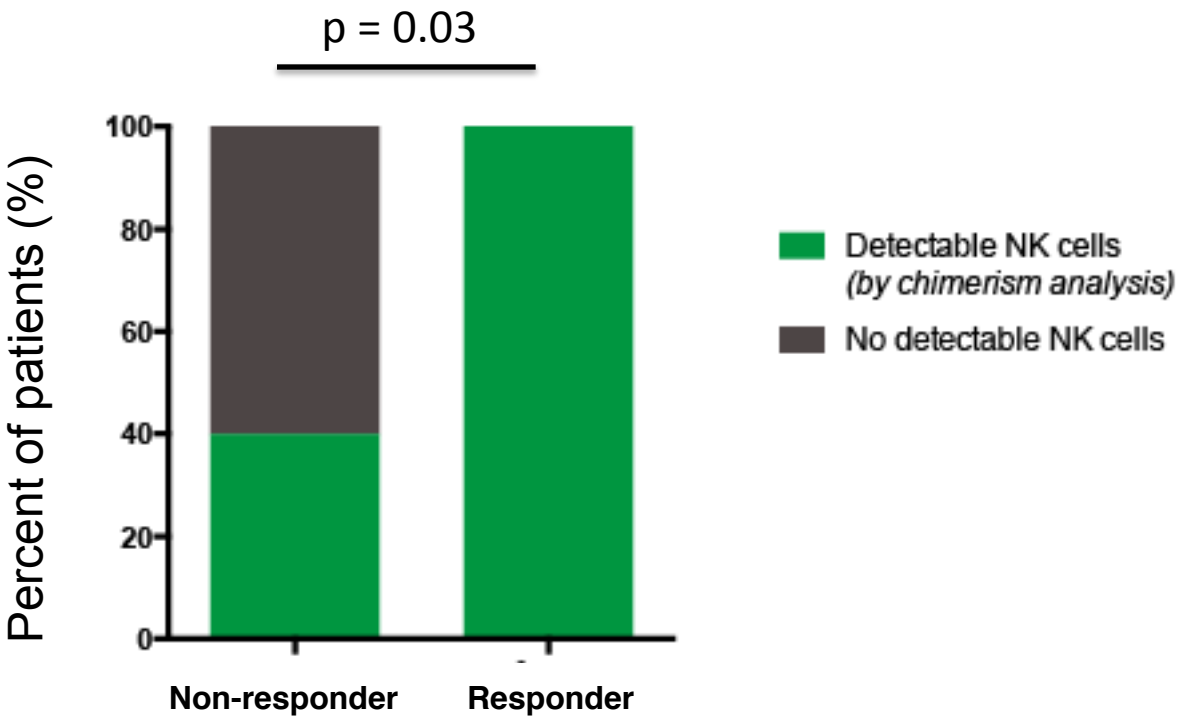


Reduction of CD34+ blast counts

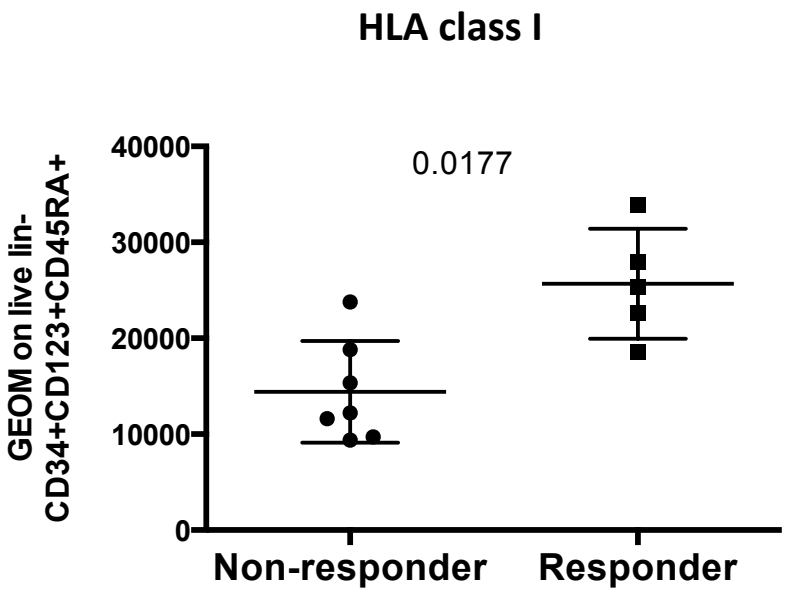


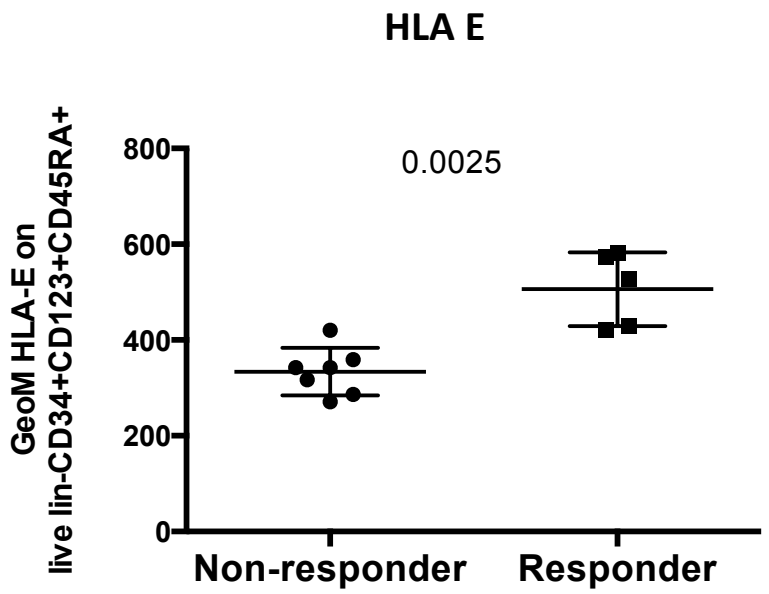
Role for NK cells in the therapeutic effect?

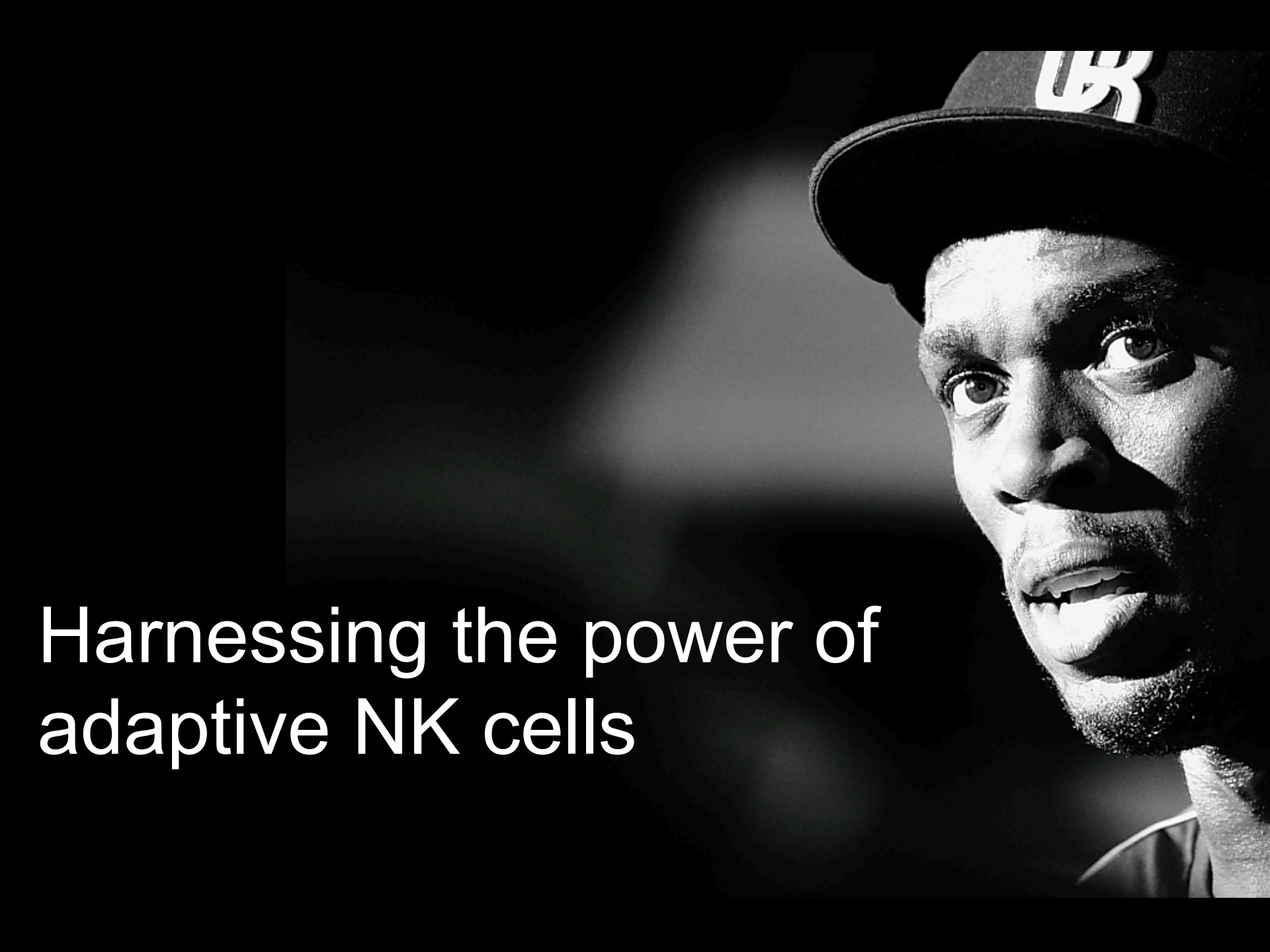
NK cell micro-chimerism at day 7-14 correlates with clinical responses



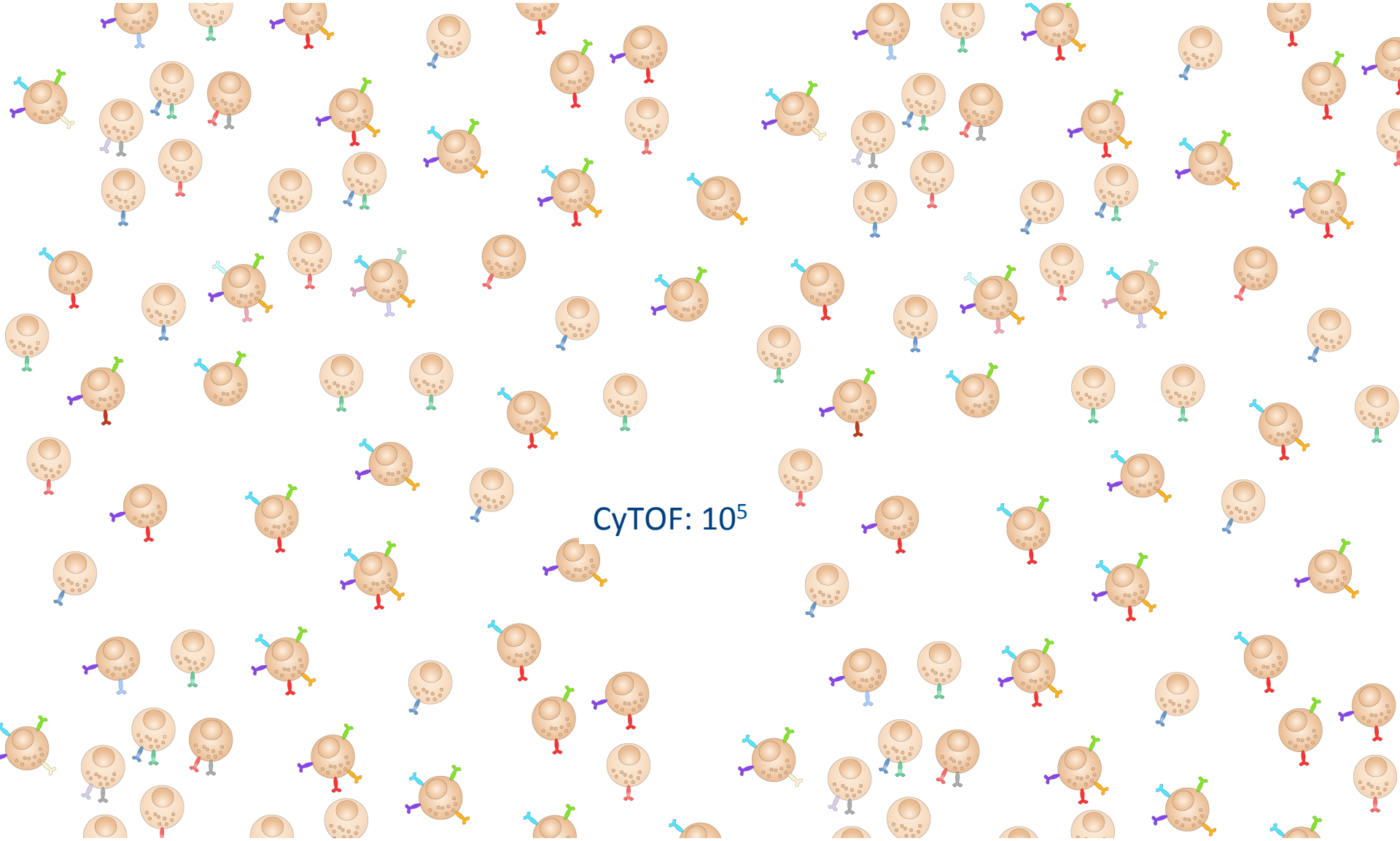
Immunoediting – higher levels of HLA class I on residual blasts in responders



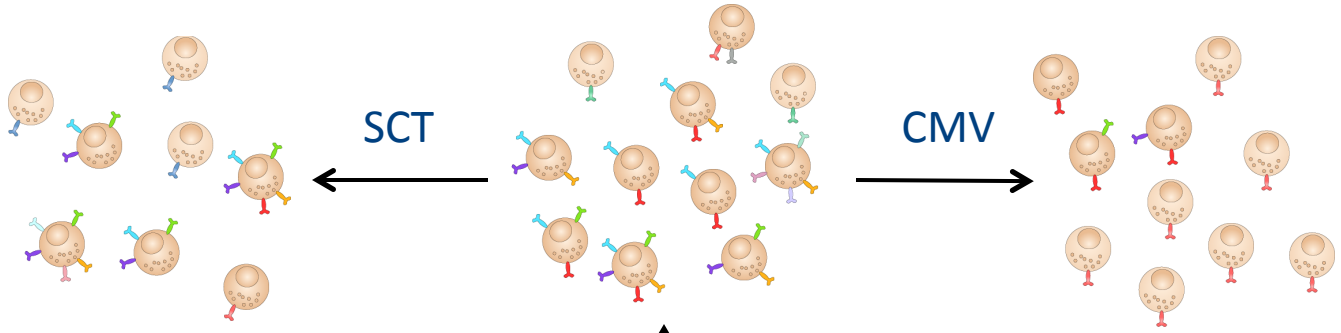


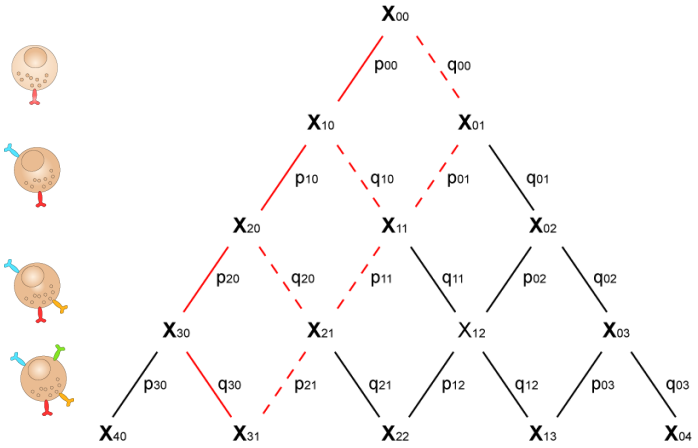

Harnessing the power of
adaptive NK cells

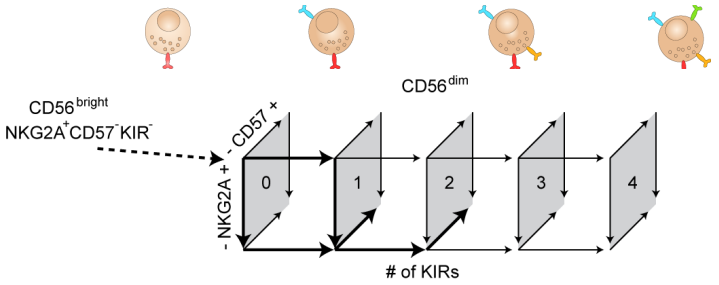
Not all NK cells are equal

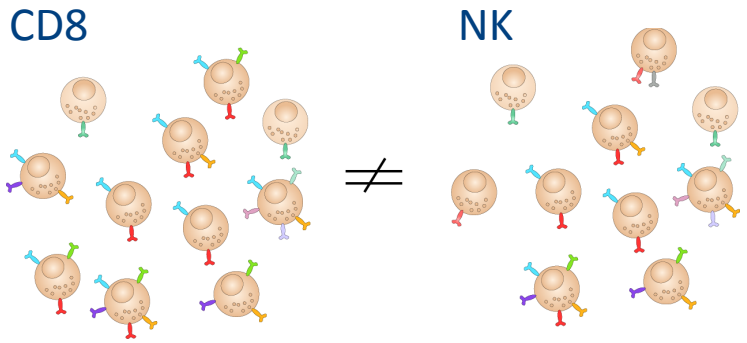


Horowitz et al., ***Science Transl. Med. 2013***









Björkström et al., ***Blood***, 2012

Björkström et al., ***Blood***, 2010

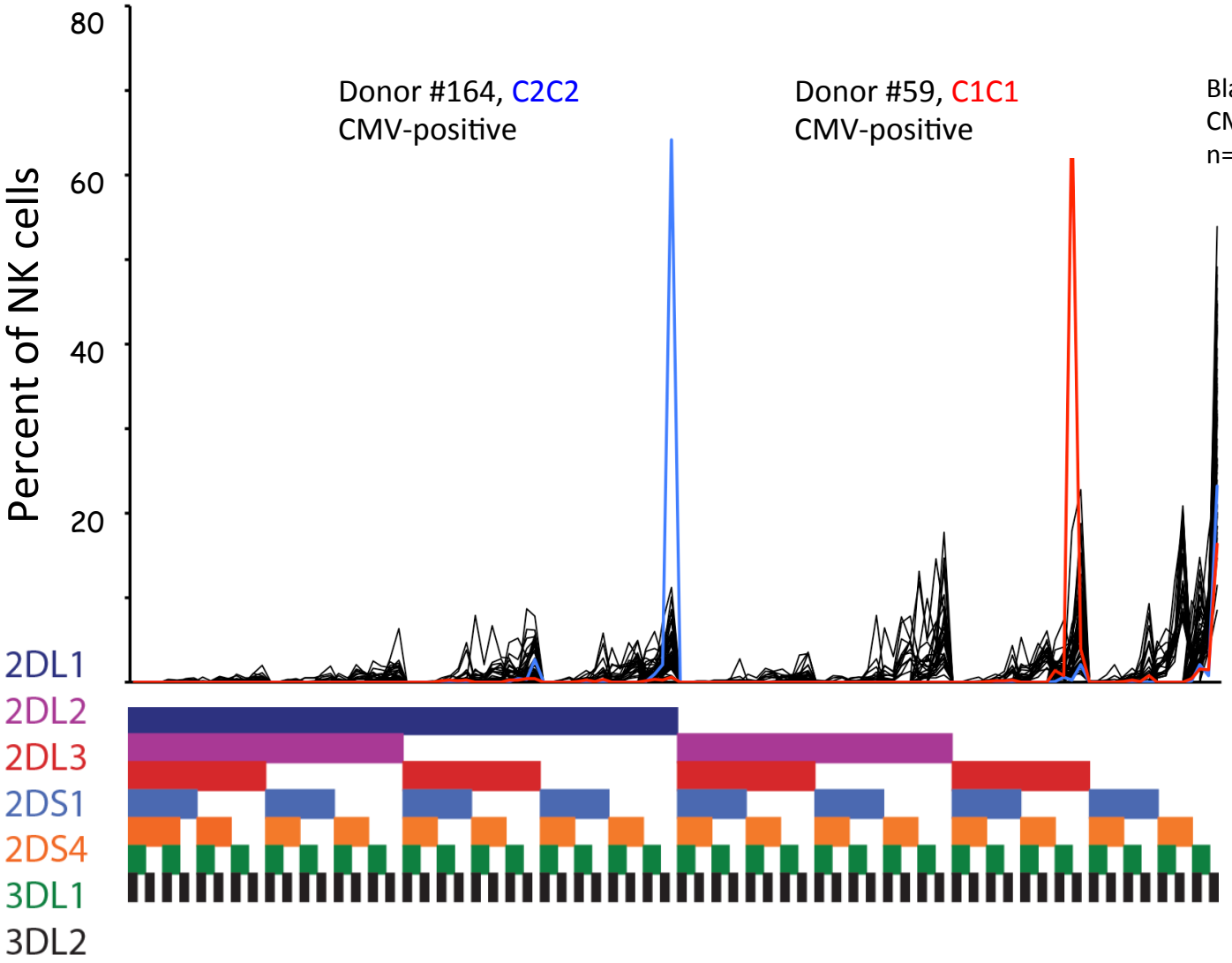
Andersson et al., ***Blood***, 2009

Björklund et al., , ***Blood***, 2010

Beziat et al., ***Blood***, 2013a

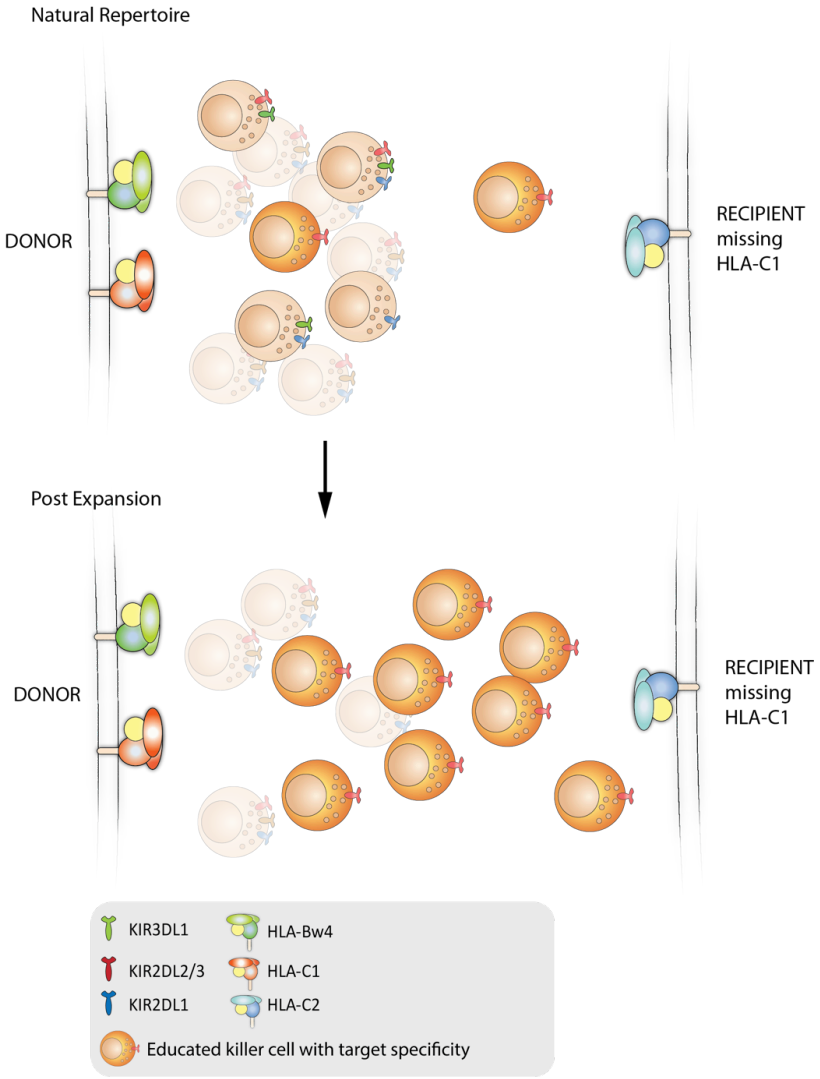
Beziat et al., ***Blood***, 2013b

CMV is associated with a clonal-like expansion of adaptive NK cells

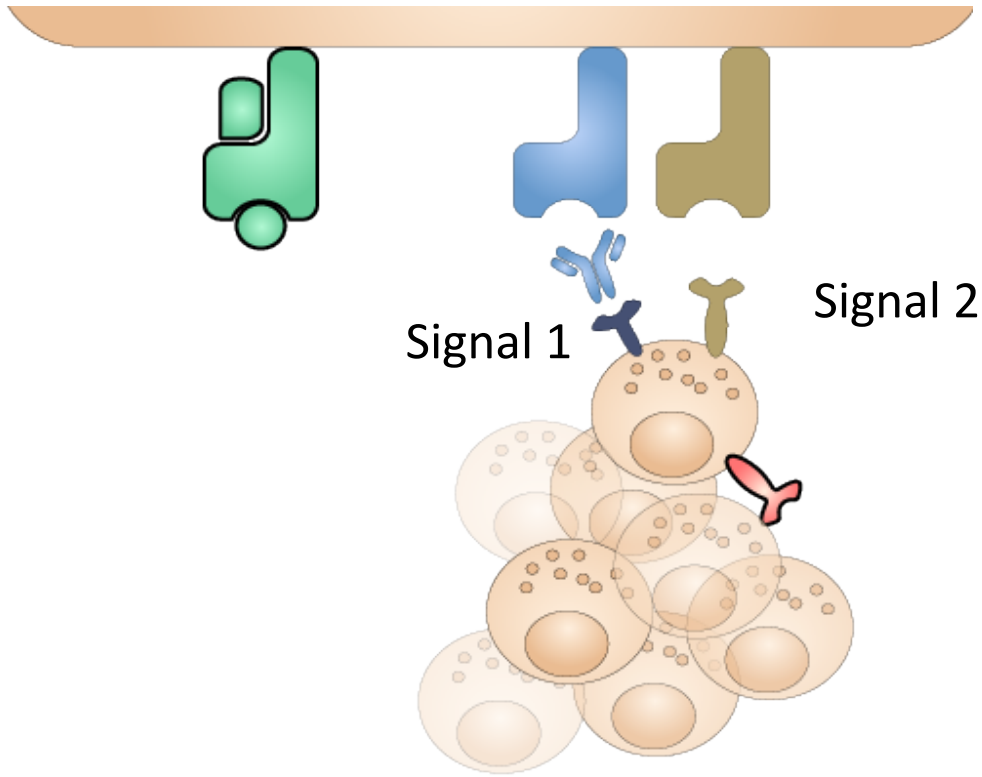


Beziat V. et al. Blood 2013

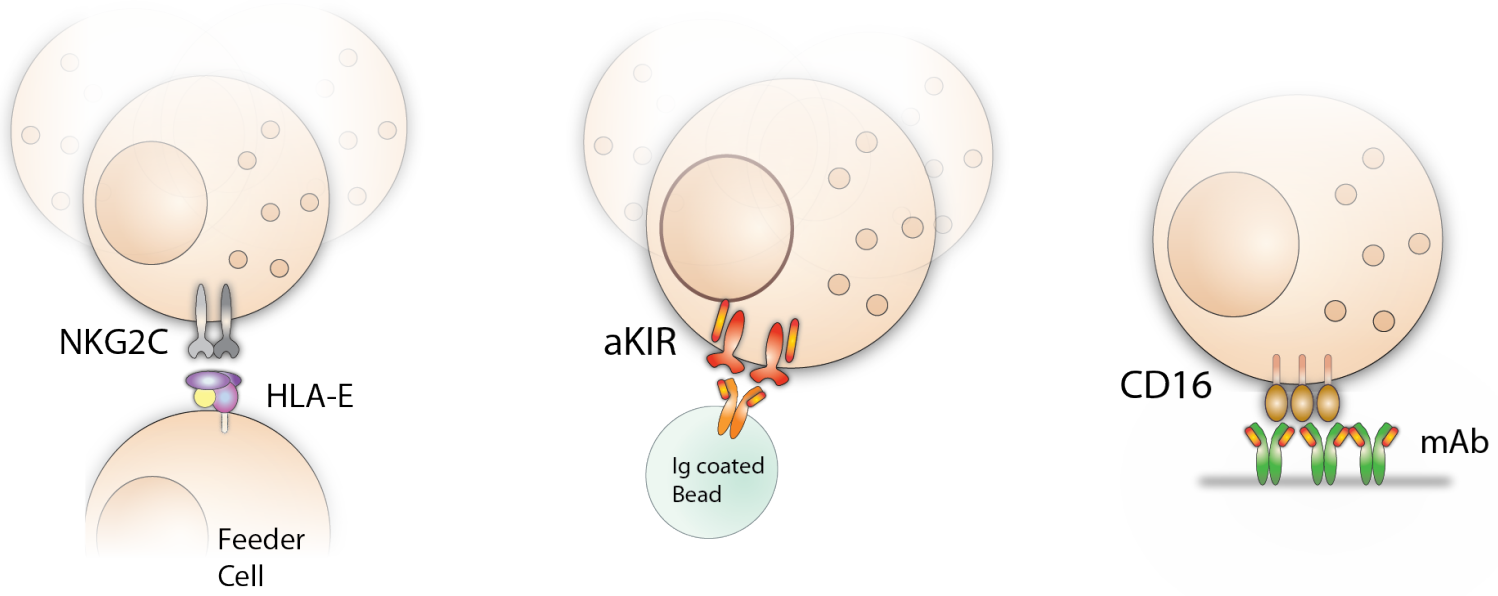
Expanding tumor-reactive NK cells



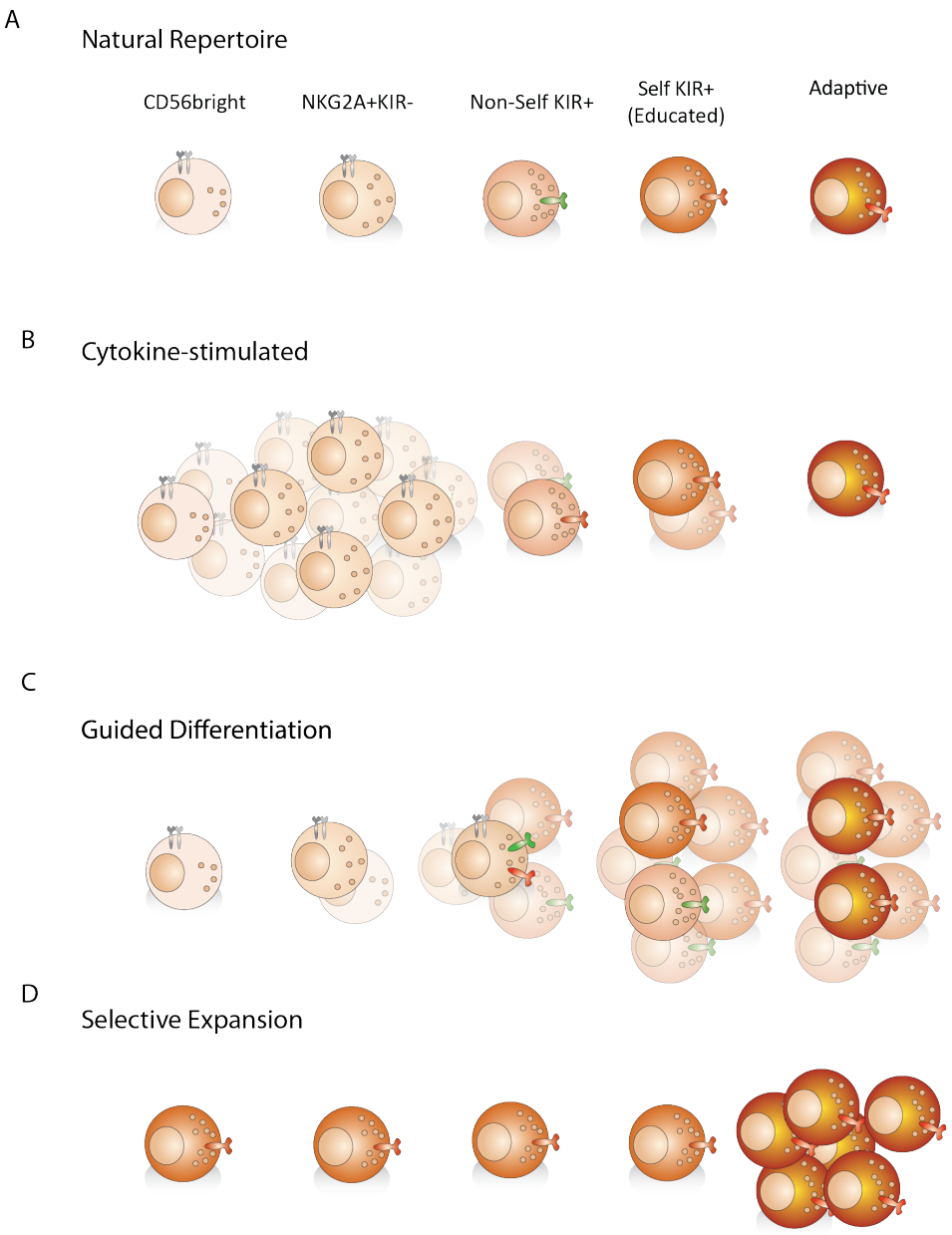
CD2 provides signal 2 in antibody-driven adaptive NK cell responses



Expansion platforms



Balancing numbers and specificity



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Malmberg group

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