



University of California
San Francisco

Graft-Versus-Host Responses, NK Cells and HIV Persistence

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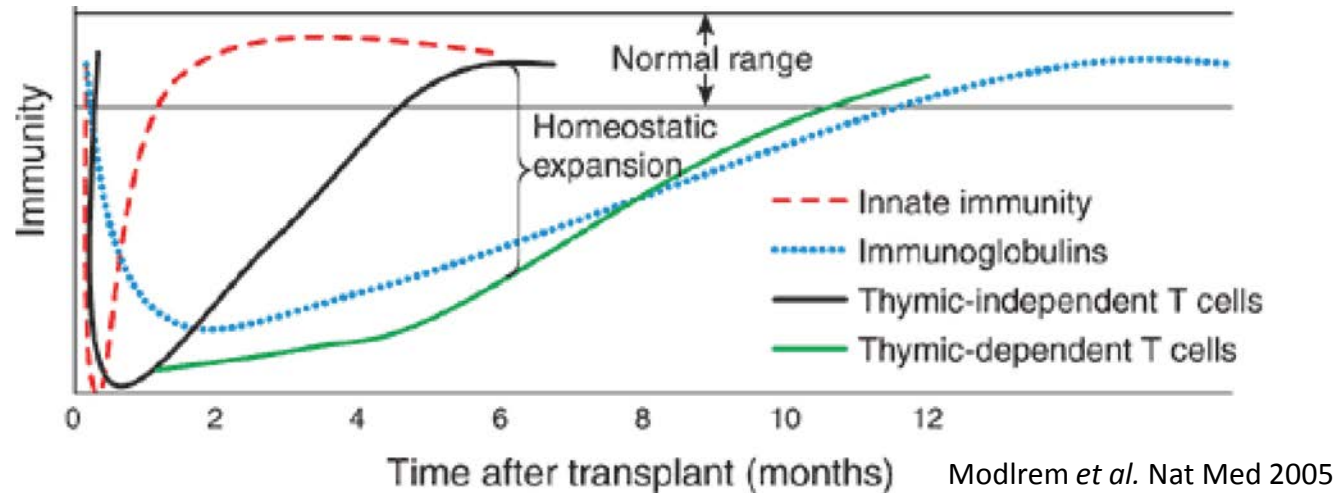
University of California San Francisco

Division of Experimental Medicine

Allogeneic HSCT and HIV-1 Persistence

- Very few strategies have led to substantial decreases in the size of the latent HIV-1 reservoir
- Allogeneic Hematopoietic Stem Cell Transplantation (HSCT) is **one of the few approaches** that can lead to sustained, significant reduction in blood and tissue HIV-1 in patients with established viral reservoirs

NK Cells Recover More Rapidly Following HSCT

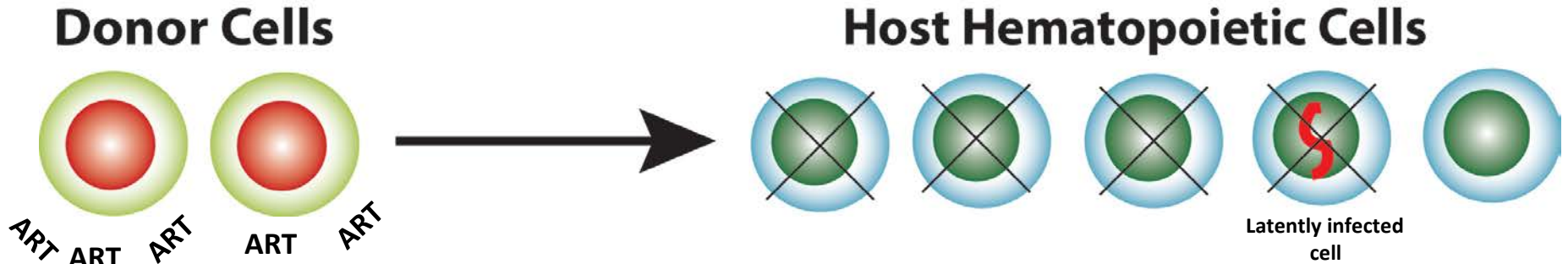


- Rapid recovery of NK cells after HSCT
- CD8 T cells and B cells take longer
- NK-cells important in the beneficial graft-versus-host-responses following allogeneic HSCT
- NK-cell infusion induces no GVHD while maintaining GVL effects

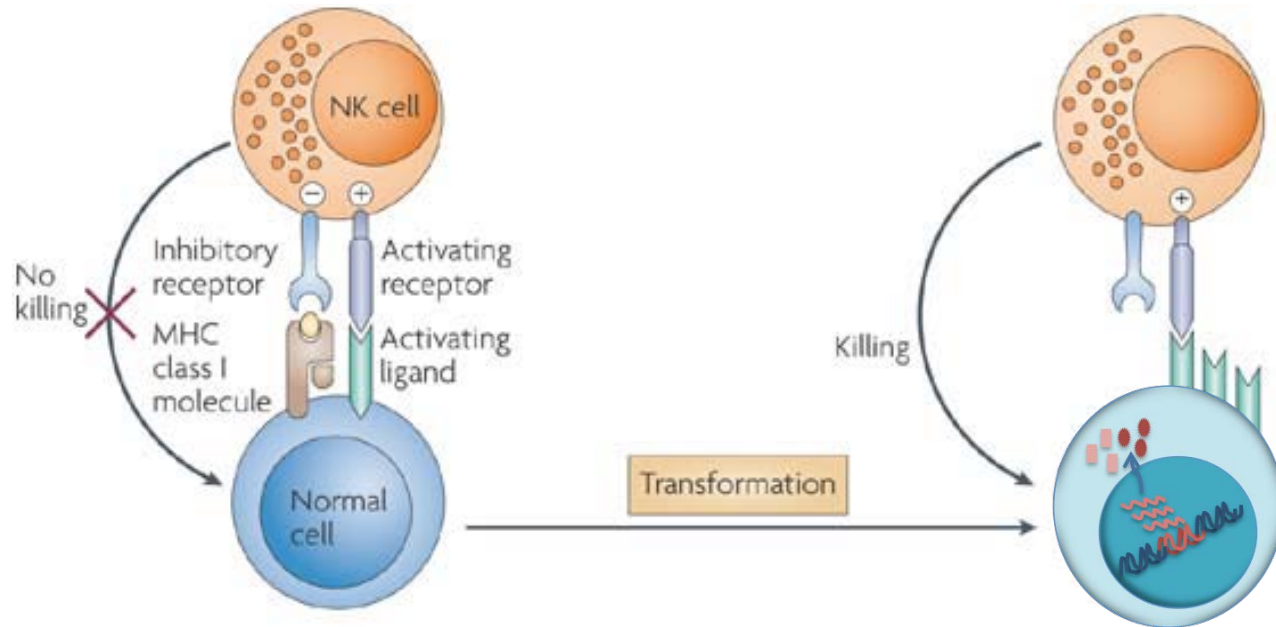
NK Cells Important in Immune Control of HIV

- NK cells from Post-Treatment Controllers have high capacity to control autologous CD4⁺ T cell HIV infection *in vitro* (Scott-Algara et al. CROI 2016)
- NK cells may also play an important role in HIV reduction following HSCT or in other therapeutic settings

Graft-Versus-HIV-1 Reservoir (GVHR)



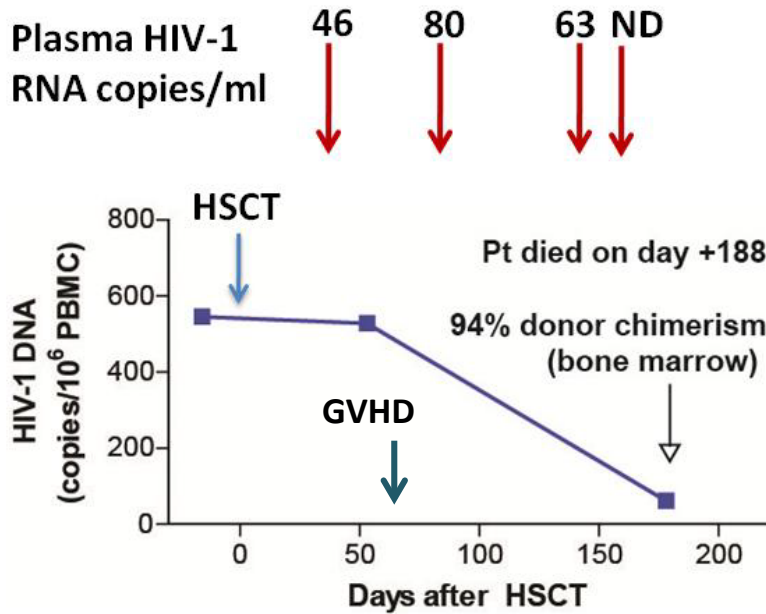
Ljunggren & Malmberg 2007



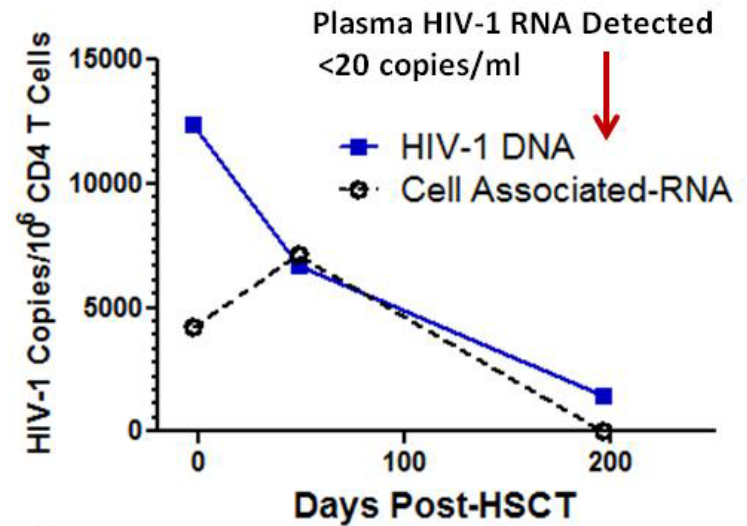
- HLA-B is downregulated by HIV-1 nef (Blais et al. 2011)

HIV-1 Reactivation Following HSCT and GVH

Pt C



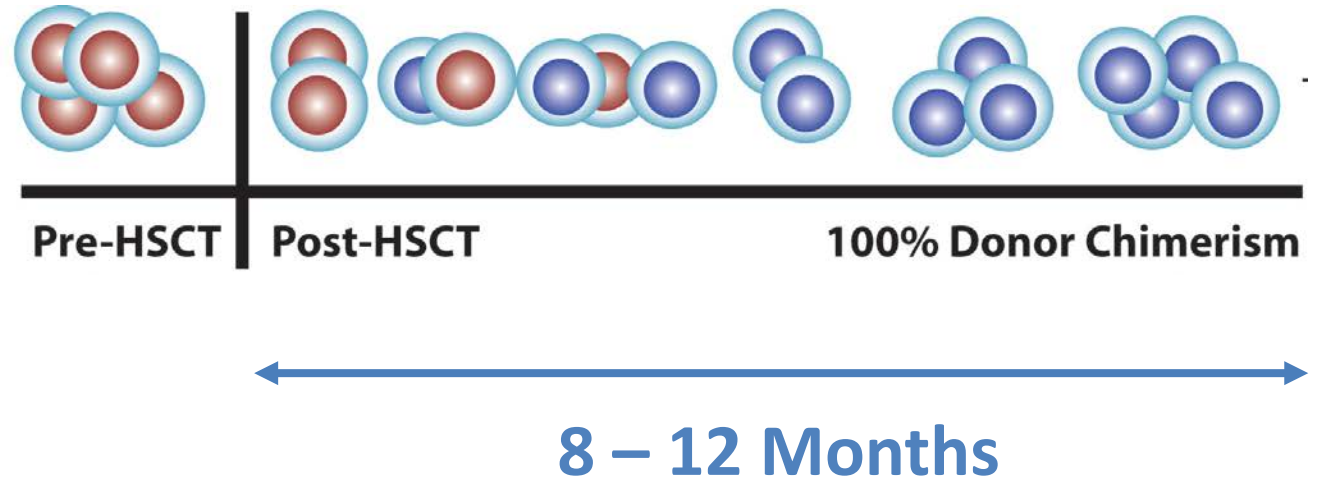
Pt D



- Does reactivation of HIV-1 provide an opportunity for NK or other immune cells to selectively target infected cells?

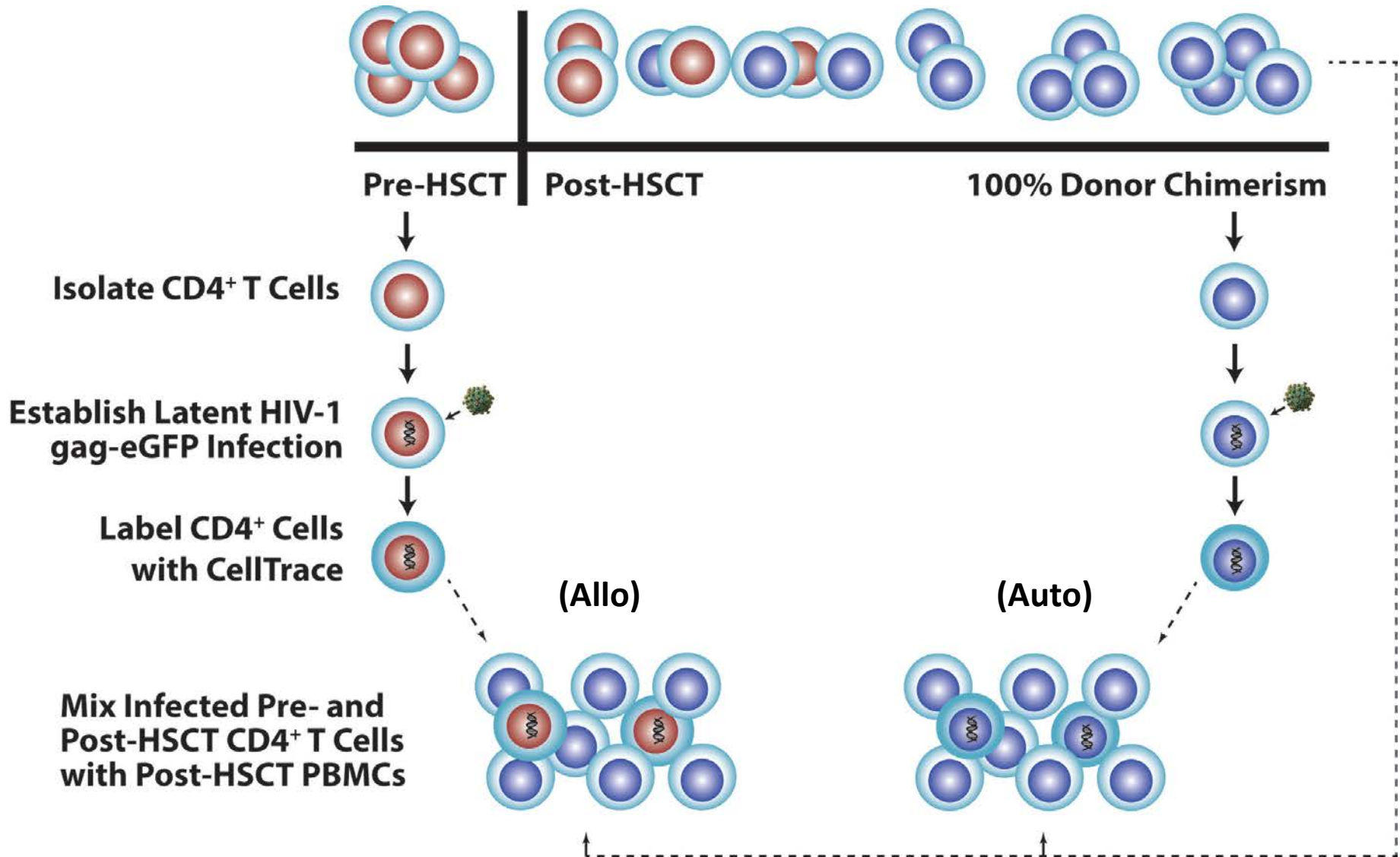
Ex Vivo GVHR Assay

Ex Vivo Determination of Graft-Versus-Residual HIV-1 Reservoir Effects



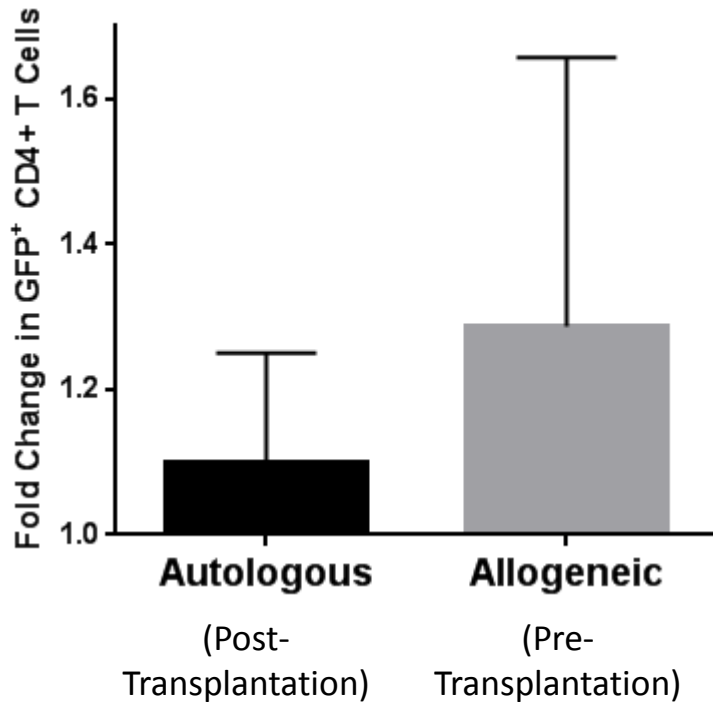
Ex Vivo GVHR Assay

Ex Vivo Determination of Graft-Versus-Residual HIV-1 Reservoir Effects



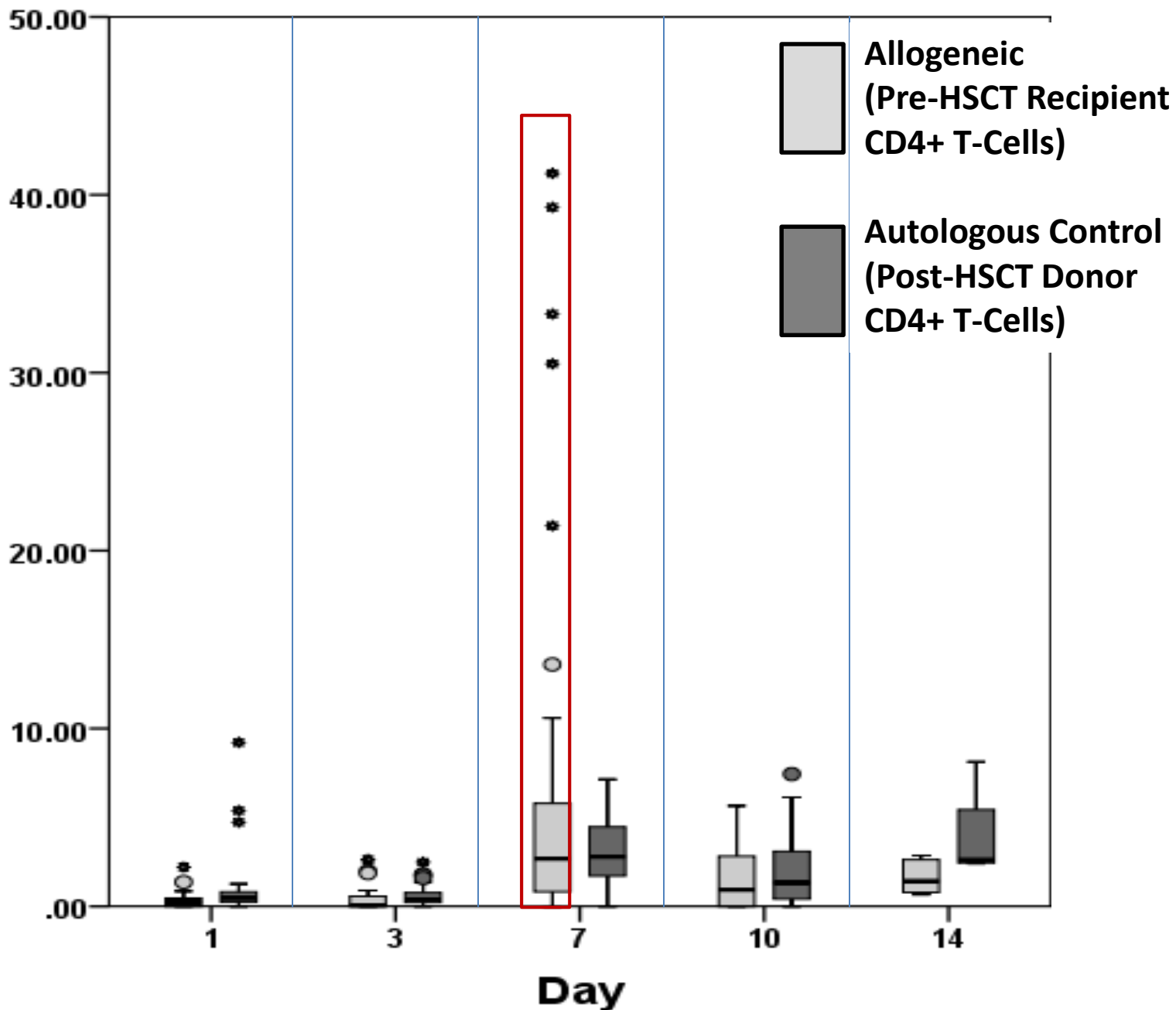
HIV-Reactivation *Ex Vivo*

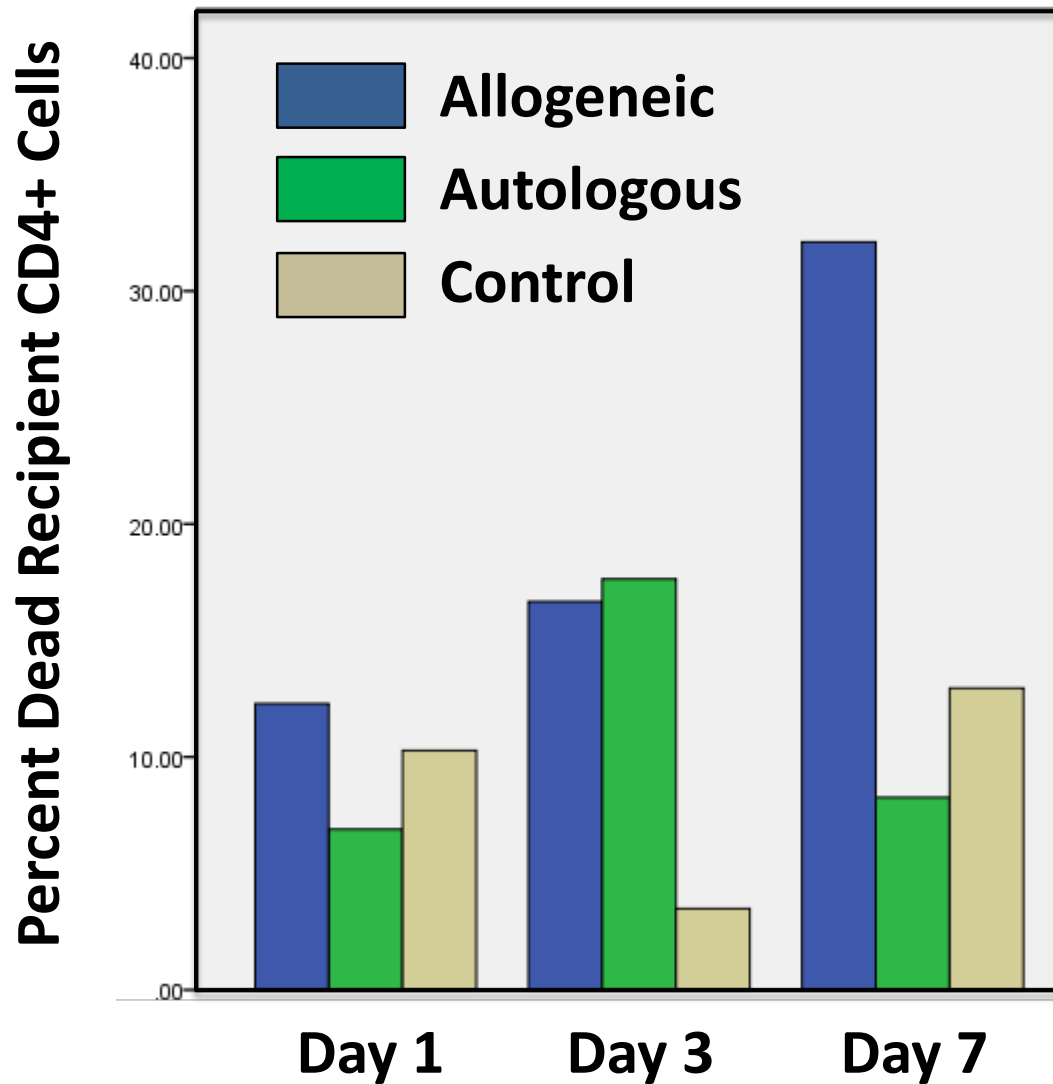
HIV-1 Reactivation After 6 Days of *Ex Vivo* Culture



Increasing frequency of less mature, less exhausted CD16^{low} NK cells

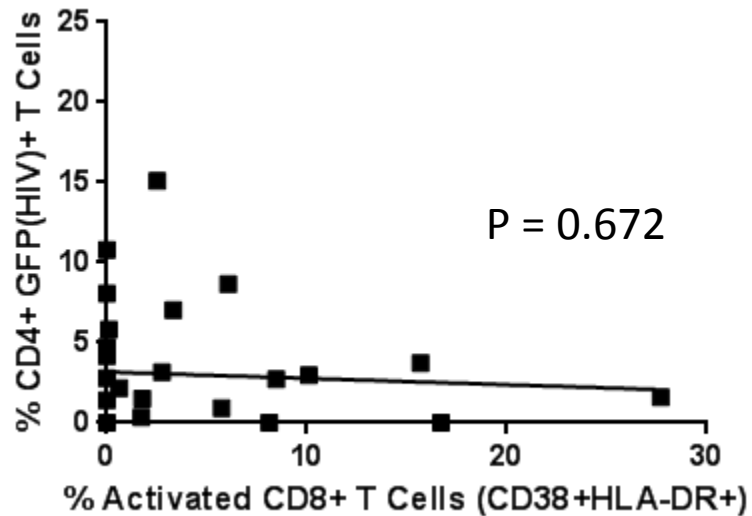
**% eGFP+ Proliferating CD4+ T-Cells
(HIV Reactivation)**



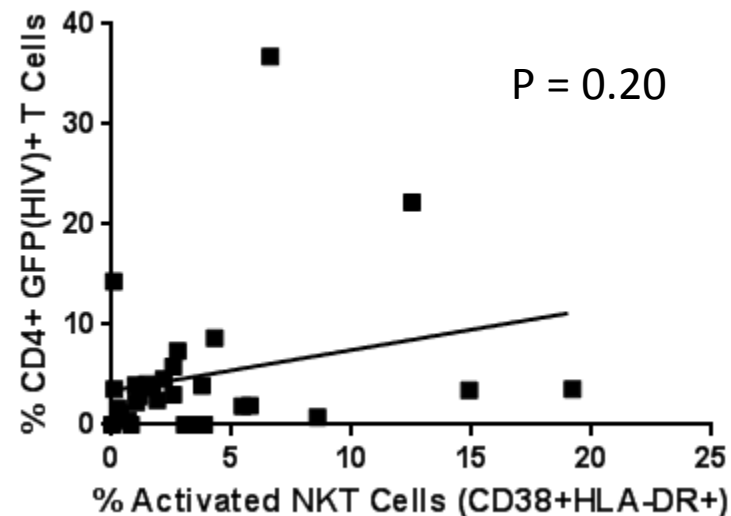
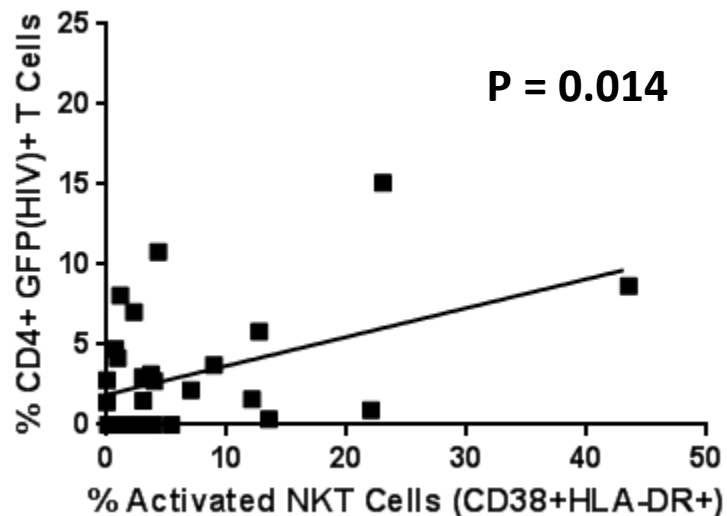
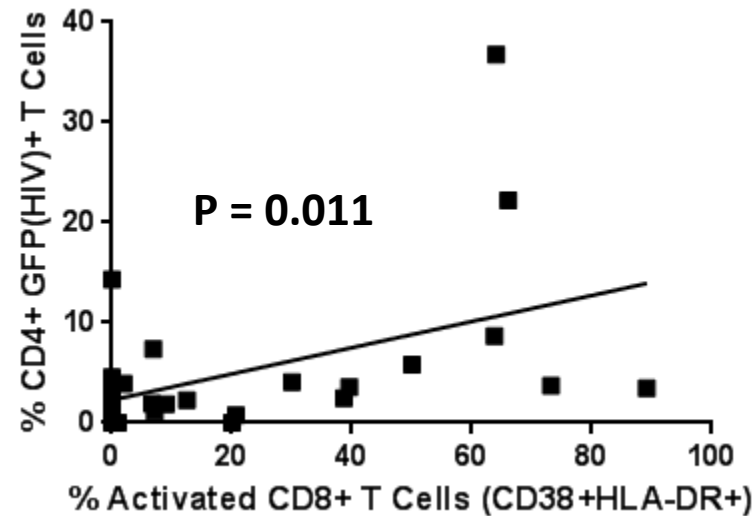


Increased CD4+ T cell death in allogeneic versus autologous experiments

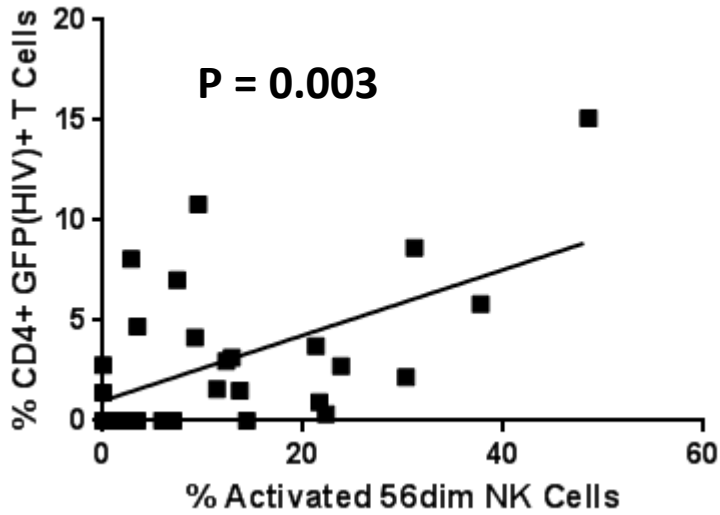
Allogeneic HLA-Matched (Pre-transplantation)



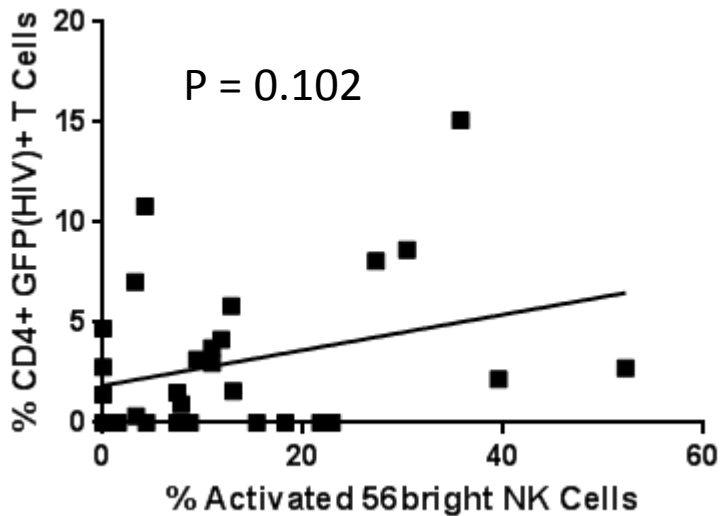
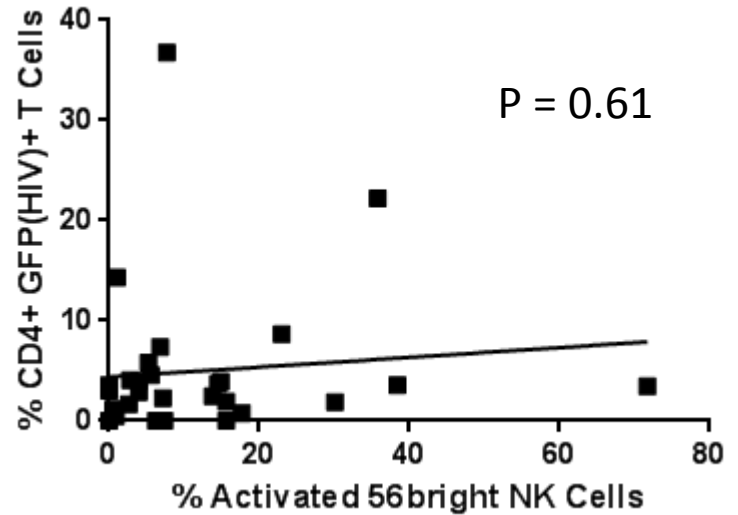
Autologous (Post-transplantation)

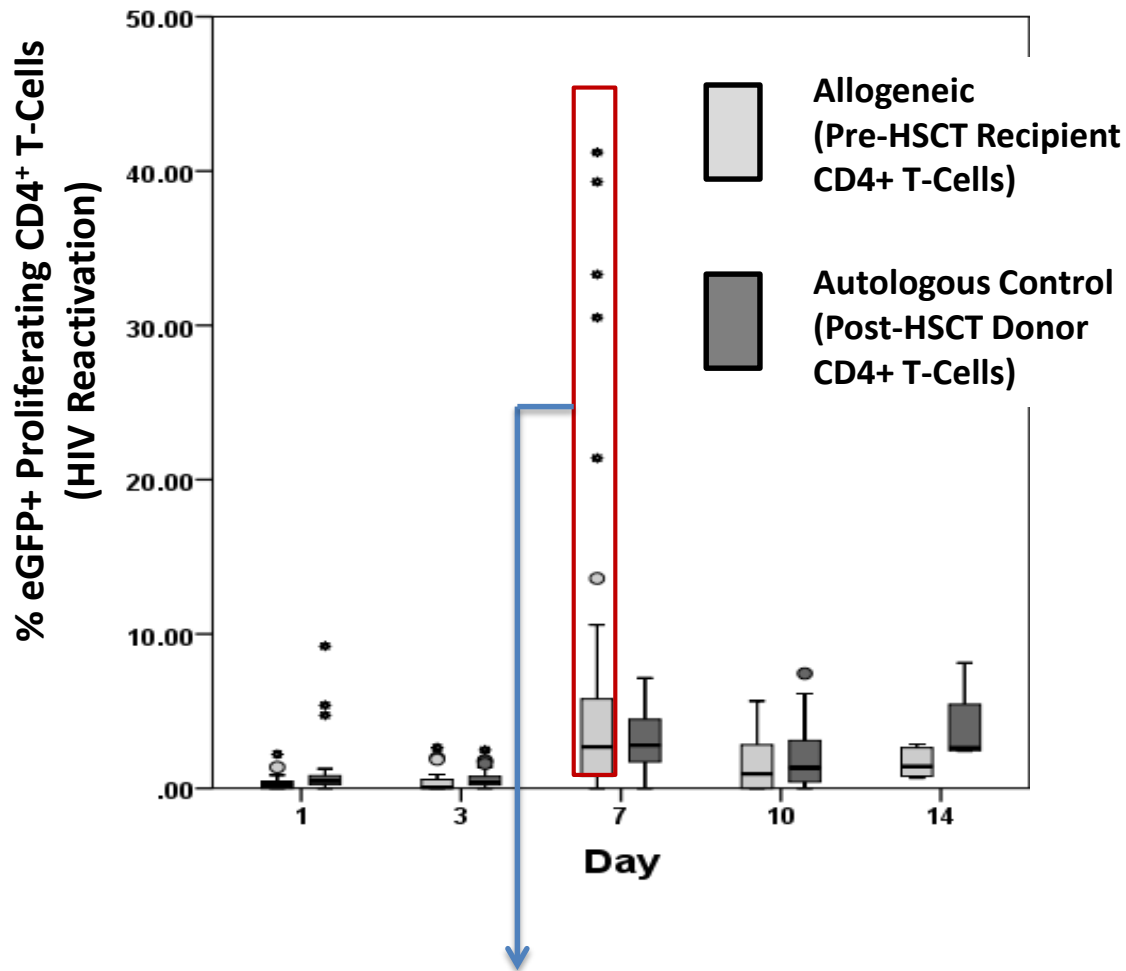


Allogeneic HLA-Matched (Pre-transplantation)



Autologous (Post-transplantation)

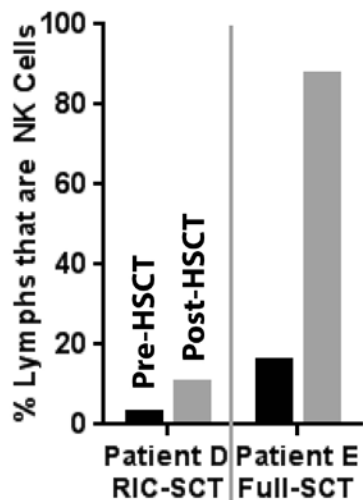




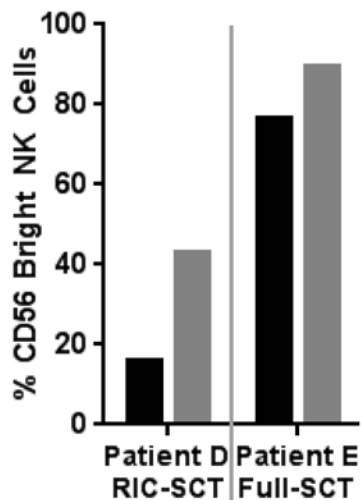
KIR-HLA interactions may play an important role in strength of allogeneic effect or HIV-specific immune targeting

NK Cell Phenotype/Function Before and After HSCT

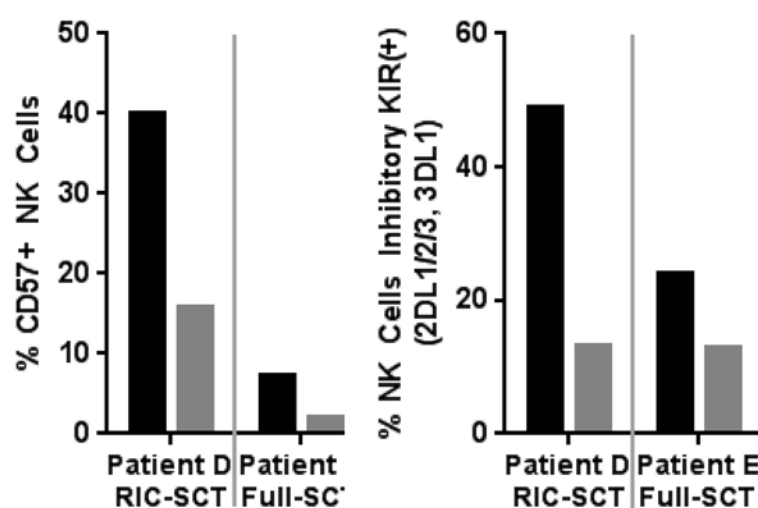
↑ NK Cell Frequency



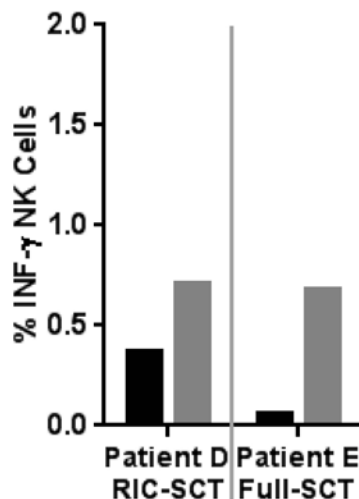
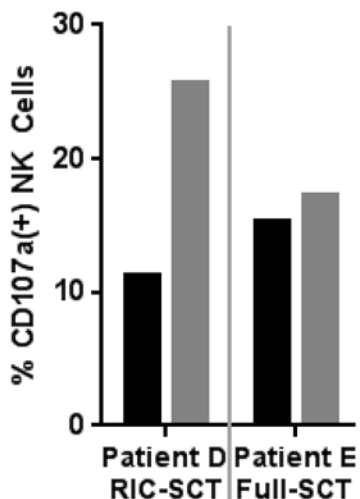
↓ Maturity and Exhaustion



↓ Inhibitory KIR Expression



↑ Cytotoxic Degranulation and INF- γ Production



■ Pre-HSCT
■ Post-HSCT

Conclusions

- Allogeneic HSCT provides important and unique insights into HIV-specific immune responses
- GVH responses may have preferential activity against HIV-1 reactivated cells
- NK and NKT cells may play an important role in targeting residual HIV reservoirs following reactivation or leading to immune control off ART

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MAKING AIDS HISTORY

