

Characterisation of Natural Killer Cell Subsets and Antibody-Dependent Cellular Cytotoxicity Function in a Case of Sustained HIV Remission After Allogeneic Stem Cell Transplantation (2nd Berlin Case)

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Disclosure: Gaebler has received support for the present manuscript from the HJH Foundation, the Hector-Foundation, the National Institutes of Health (REACH Delaney grant UM1 AI164565 subaward), and the DZIF (German Center for Infection Research, TTU 04.823); honoraria for lectures from GSK; support for attending meetings from Gilead; and is a Charité-Foundation Recruiting Grantee. Hoelzemer has received support for the present manuscript from the Federal Ministry of Research, Technology and Space (01KI2110), the iSTAR

program from the Federal Ministry of Research, Technology and Space, and the DZIF (German Center for Infection Research, TTU 04.823). Penack has received grants from José Carreras Leukämie-Stiftung (23R/2021), Deutsche Krebshilfe (70113519), Deutsche Forschungsgemeinschaft (PE 1450/7-1, PE 1450/9-1, PE 1450/10-1, PE 1450/11-1) and Stiftung Charité BIH (BIH_PRO_549, Focus Group Vascular Biomedicine), with payments to the institution; consulting fees from Apogepha, Alexion, Equillum Bio, Jazz, Gilead, Novartis, MSD, Omeros, Orca Bio, Priothera, Sanofi, Shionogi, and SOBI; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Alexion, Gilead, Jazz, MSD, Neovii, Novartis, Pfizer, and Therakos; research support from Incyte, Gilead, and Priothera outside of the present manuscript; holds a leadership or fiduciary role as the Chairperson of the EBMT Transplant Complications Working Party; and holds stock/stock options in Orca Bio. Gruell has received payments from the University of Cologne for licensed patent applications relating to HIV neutralising antibodies. Trenkner has received support for the present manuscript from the Federal Ministry of Research, Technology and Space (01KI2110). Schommers has received support for the present manuscript from the German Research Foundation (DFG, Emmy Noether Program Nr. 495793173), the Else Kröner Fresenius Foundation (EKFS), and the German Center for Infection Research (DZIF); and payments from the University of Cologne for licensed patent applications relating to HIV neutralising antibodies. Kraus has received support for the present manuscript from the Federal Ministry of Research, Technology and Space (01KI2110). Kor has declared no conflicts of interest.

Acknowledgements: The authors thank the second Berlin patient (B2) and all study participants for their willingness to collaborate, and Quirin Hammer for their assistance with the design of the adaptive NK cell panels.

Keywords: Allogeneic stem cell transplant, antibody-dependent cellular cytotoxicity (ADCC), HIV cure, HIV remission, natural killer (NK) cells.

Citation: EMJ Microbiol Infect Dis. 2025;6[Suppl 4]:26-28. <https://doi.org/10.33590/emjmicrobio-infectdis/RZQG5710>

BACKGROUND AND AIMS

Natural killer (NK) cells are increasingly studied in HIV cure research as certain subsets have been linked to natural HIV control, enhanced antibody-dependent cellular cytotoxicity (ADCC), and reduced viral reservoirs.¹⁻⁶ Elite controllers (EC) often display higher envelope (Env)-specific ADCC activity,⁷ and the only moderately successful HIV vaccine trial to date, RV144, identified ADCC as a correlate of reduced acquisition risk.⁸

sustained HIV remission after allogeneic stem cell transplantation with heterozygous *CCR5*Δ32 donor cells. Peripheral blood mononuclear cells were genotyped for killer-Ig-like receptor genes, and NK cells were analysed by multiparameter flow cytometry, as well as standardised ADCC assays, against rituximab-coated target cells. HIV-1-specific ADCC capacity was tested in longitudinal plasma samples from B2, employing a degranulation assay against immobilised Env protein, in comparison with plasma from ECs and broadly neutralising antibodies (Figure 1).

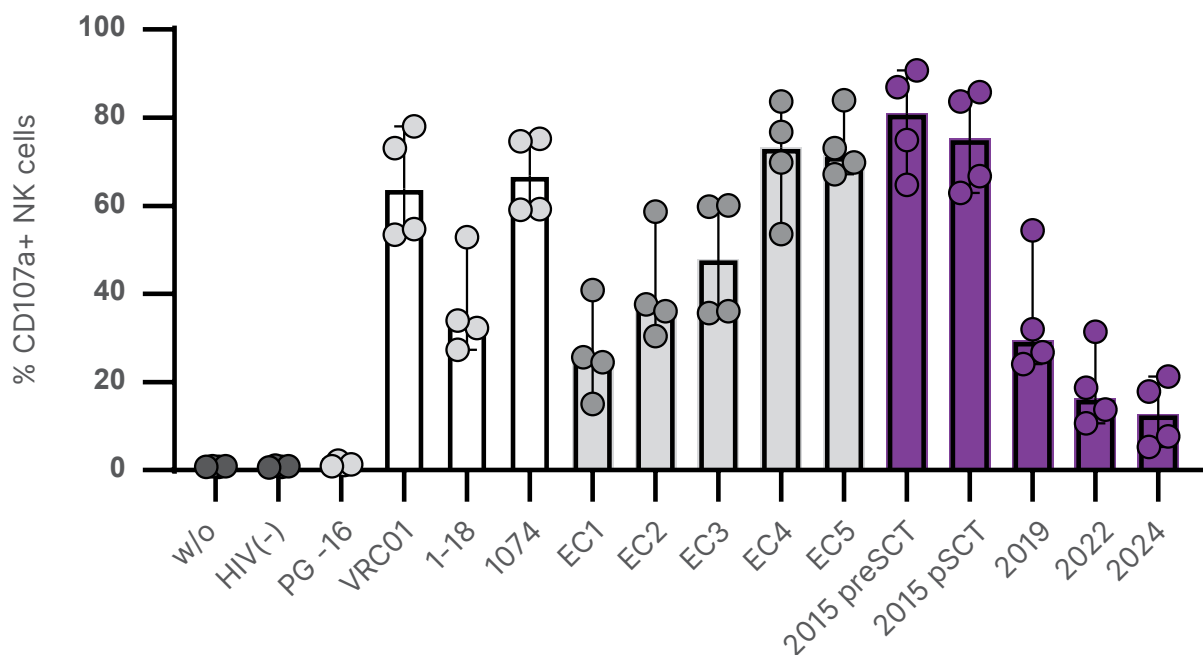
METHODS

Based on these findings, the authors performed in-depth phenotyping and functional testing of NK cells from the second Berlin individual (B2), who displayed

RESULTS

B2 displayed an NK cell phenotype with a markedly higher frequency of natural killer group 2 member A (NKG2A)⁺ cluster of

Figure 1: HIV-specific antibody-dependent cellular cytotoxicity activity of the second Berlin individual's plasma.



Summary of cumulative ADCC responses. NK cells (N=4 biological replicates) were incubated with Env-coated wells treated with PBS, plasma from a donor who is HIV-negative (1:1000 dilution; black), bnAbs (PG-16, 1-18, VRC01, and 10-74; 10 µg/mL; white), plasma from five ECs (1:1000; dark grey), or longitudinal B2 plasma samples (1:1000 dilution; purple). The bar shows the median with the IQR.

ADCC: antibody-dependent cellular cytotoxicity; B2: second Berlin individual; bnAbs: broadly neutralising antibodies; CD: cluster of differentiation; EC: elite controllers; Env: envelope; IQR: interquartile range; NK: natural killer; PBS: phosphate-buffered saline; SCT: stem cell transplant; w/o: without.

differentiation (CD)57⁺ NK cells compared to controls who were HIV-negative and cytomegalovirus-positive, and previously published data on allogeneic stem cell transplantation recipients.⁹ This subset did not undergo downmodulation of promyelocytic leukaemia zinc finger and Fc ϵ receptor γ chain characteristics of adaptive-like NK cells, but nonetheless contributed substantially to ADCC-activity upon encountering rituximab-coated targets. Around transplantation, B2's plasma mediated high HIV-specific ADCC activity, surpassing EC plasma (N=5) and monoclonal broadly neutralising antibodies. ADCC activity mediated by B2's plasma declined substantially in the years following transplantation (Figure 1).

CONCLUSION

Taken together, the authors observed an NK cell phenotype in B2 characterised by the expansion of mature NKG2A⁺ NK cells, alongside potent HIV-specific plasma ADCC activity. These data, together with findings from the first case of HIV-1 remission after transplantation with wild-type *CCR5* donor cells (the Geneva Case),¹⁰ suggest a potential contribution of NK cell-mediated mechanisms to modulate the HIV reservoir, independent of *CCR5* Δ 32 homozygosity.

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