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T and NK cell immunity after hematopoietic stem cell transplantation

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References

1. Copelan EA. Hematopoietic stem-cell transplantation. *N Engl J Med.* 2006;354:1813-1826.
2. Gatti RA, Meuwissen HJ, Allen HD, Hong R, Good RA. Immunological reconstitution of sex-linked lymphopenic immunological deficiency. *Lancet* 1968;2:1366-1369.
3. De Koning J, van Bekkum DW, Dickey KA et al. Transplantation of bone-marrow cells and fetal thymus in an infant with lymphopenic immunological deficiency. *Lancet* 1969;1:1223-1227.
4. Juric MK, Ghimire S, Ogonek J et al. Milestones of Hematopoietic Stem Cell Transplantation - From First Human Studies to Current Developments. *Front Immunol.* 2016;7:470.
5. Passweg JR, Baldomero H, Bader P et al. Hematopoietic stem cell transplantation in Europe 2014: more than 40 000 transplants annually. *Bone Marrow Transplant* 2016;51:786-792.
6. Thomas ED, Buckner CD, Banaji M et al. One hundred patients with acute leukemia treated by chemotherapy, total body irradiation, and allogeneic marrow transplantation. *Blood* 1977;49:511-533.
7. Thomas ED, Storb R, Fefer A et al. Aplastic anaemia treated by marrow transplantation. *Lancet* 1972;1:284-289.
8. Lucarelli G, Isgro A, Sodani P, Gaziev J. Hematopoietic stem cell transplantation in thalassemia and sickle cell anemia. *Cold Spring Harb Perspect Med.* 2012;2:a011825.
9. Hansen JA, Clift RA, Thomas ED et al. Transplantation of marrow from an unrelated donor to a patient with acute leukemia. *N Engl J Med.* 1980;303:565-567.
10. Beatty PG, Clift RA, Mickelson EM et al. Marrow transplantation from related donors other than HLA-identical siblings. *N Engl J Med.* 1985;313:765-771.
11. Gluckman E, Broxmeyer HA, Auerbach AD et al. Hematopoietic reconstitution in a patient with Fanconi's anemia by means of umbilical-cord blood from an HLA-identical sibling. *N Engl J Med.* 1989;321:1174-1178.
12. Reisner Y, Kapoor N, Kirkpatrick D et al. Transplantation for severe combined immunodeficiency with HLA-A,B,D,DR incompatible parental marrow cells fractionated by soybean agglutinin and sheep red blood cells. *Blood* 1983;61:341-348.
13. Russell NH, Hunter A, Rogers S, Hanley J, Anderson D. Peripheral blood stem cells as an alternative to marrow for allogeneic transplantation. *Lancet* 1993;341:1482.
14. Petersdorf EW. Risk assessment in haematopoietic stem cell transplantation: histocompatibility. *Best Pract Res Clin Haematol.* 2007;20:155-170.
15. Feng X, Hui KM, Younes HM, Brickner AG. Targeting minor histocompatibility antigens in graft versus tumor or graft versus leukemia responses. *Trends Immunol.* 2008;29:624-632.
16. Devergie A. Graft versus host disease. In: Apperley J, Carreras E, Gluckman E, Gratwohl A, Masszi T, eds. *Haematopoietic Stem Cell Transplantation*. Genova: Forum Service Editore; 2008:218-235.
17. Locatelli F, Lucarelli B, Merli P. Current and future approaches to treat graft failure after allogeneic hematopoietic stem cell transplantation. *Expert Opin Pharmacother.* 2014;15:23-36.
18. Klein J, Sato A. The HLA system. First of two parts. *N Engl J Med.* 2000;343:702-709.
19. van Rood JJ, Oudshoorn M. Eleven million donors in Bone Marrow Donors Worldwide! Time for reassessment? *Bone Marrow Transplant* 2008;41:1-9.
20. Gragert L, Eapen M, Williams E et al. HLA match likelihoods for hematopoietic stem-cell grafts in the U.S. registry. *N Engl J Med.* 2014;371:339-348.
21. World Marrow Donor Association. Bone Marrow Donors Worldwide. <https://www.bmdw.org> . 2017.
22. van Walraven SM, Brand A, Bakker JN et al. The increase of the global donor inventory is of limited benefit to patients of non-Northwestern European descent. *Haematologica* 2017;102:176-183.
23. Reisner Y, Hagin D, Martelli MF. Haploidentical hematopoietic transplantation: current status and future perspectives. *Blood* 2011;118:6006-6017.
24. Larghero J, Garcia J, Gluckman E. Sources and procurement of stem cells. In: Apperley J, Carreras E, Gluckman E, Gratwohl A, Masszi T, eds. *Haematopoietic Stem Cell Transplantation*. Genova: Forum Service Editore; 2008:112-127.
25. Ruggeri A, Paviglianiti A, Gluckman E, Rocha V. Impact of HLA in cord blood transplantation outcomes. *HLA* 2016;87:413-421.
26. Anasetti C, Logan BR, Lee SJ et al. Peripheral-blood stem cells versus bone marrow from unrelated donors. *N Engl J Med.* 2012;367:1487-1496.
27. Gratwohl A. Principles of conditioning. In: Apperley J, Carreras E, Gluckman E, Gratwohl A, Masszi T, eds. *Haematopoietic Stem Cell Transplantation*. Genova: Forum Service Editore; 2008:128-144.

28. ten Brink MH, Zwaveling J, Swen JJ et al. Personalized busulfan and treosulfan conditioning for pediatric stem cell transplantation: the role of pharmacogenetics and pharmacokinetics. *Drug Discov.Today* 2014;19:1572-1586.
29. Mohty M. Mechanisms of action of antithymocyte globulin: T-cell depletion and beyond. *Leukemia* 2007;21:1387-1394.
30. Admiraal R, van Kesteren C, Jol-van der Zijde CM et al. Association between anti-thymocyte globulin exposure and CD4+ immune reconstitution in paediatric haemopoietic cell transplantation: a multicentre, retrospective pharmacodynamic cohort analysis. *Lancet Haematol.* 2015;2:e194-e203.
31. Rebello P, Cwynarski K, Varughese M et al. Pharmacokinetics of CAMPATH-1H in BMT patients. *Cytotherapy*. 2001;3:261-267.
32. Waller EK, Langston AA, Lonial S et al. Pharmacokinetics and pharmacodynamics of anti-thymocyte globulin in recipients of partially HLA-matched blood hematopoietic progenitor cell transplantation. *Biol.Blood Marrow Transplant* 2003;9:460-471.
33. Willemse L, Jol-van der Zijde CM, Admiraal R et al. Impact of serotherapy on immune reconstitution and survival outcomes after stem cell transplants in children: thymoglobulin versus alemtuzumab. *Biol.Blood Marrow Transplant* 2015;21:473-482.
34. Storb R, Antin JH, Cutler C. Should methotrexate plus calcineurin inhibitors be considered standard of care for prophylaxis of acute graft-versus-host disease? *Biol.Blood Marrow Transplant* 2010;16:S18-S27.
35. Vossen JM, Guiot HF, Lankester AC et al. Complete suppression of the gut microbiome prevents acute graft-versus-host disease following allogeneic bone marrow transplantation. *PLoS.One.* 2014;9:e105706.
36. Mathewson ND, Jenq R, Mathew AV et al. Gut microbiome-derived metabolites modulate intestinal epithelial cell damage and mitigate graft-versus-host disease. *Nat.Immunol.* 2016;17:505-513.
37. Cwynarski K, Ainsworth J, Cobbold M et al. Direct visualization of cytomegalovirus-specific T-cell reconstitution after allogeneic stem cell transplantation. *Blood* 2001;97:1232-1240.
38. Heemskerk B, Lankester AC, van VT et al. Immune reconstitution and clearance of human adenovirus viremia in pediatric stem-cell recipients. *J.Infect.Dis.* 2005;191:520-530.
39. Annels NE, Kalpoe JS, Bredius RG et al. Management of Epstein-Barr virus (EBV) reactivation after allogeneic stem cell transplantation by simultaneous analysis of EBV DNA load and EBV-specific T cell reconstitution. *Clin.Infect.Dis.* 2006;42:1743-1748.
40. Ahmad N, Drew WL, Lagunoff M. Herpesviruses. In: Ryan KJ, Ray CJ, eds. Sherris Medical Microbiology. New York: McGraw-Hill Education, Inc; 2014:245-270.
41. van Tol MJ, Claas EC, Heemskerk B et al. Adenovirus infection in children after allogeneic stem cell transplantation: diagnosis, treatment and immunity. *Bone Marrow Transplant.* 2005;35:S73-S76.
42. Gottschalk S, Rooney CM, Heslop HE. Post-transplant lymphoproliferative disorders. *Annu.Rev.Med.* 2005;56:29-44.
43. Ljungman P, Hakki M, Boeckh M. Cytomegalovirus in hematopoietic stem cell transplant recipients. *Hematol.Oncol.Clin.North Am.* 2011;25:151-169.
44. Renaud C, Englund JA. Antiviral therapy of respiratory viruses in haematopoietic stem cell transplant recipients. *Antivir.Ther.* 2012;17:175-191.
45. Ljungman P. Molecular monitoring of viral infections after hematopoietic stem cell transplantation. *Int.J.Hematol.* 2010;91:596-601.
46. Boeckh M, Nichols WG. The impact of cytomegalovirus serostatus of donor and recipient before hematopoietic stem cell transplantation in the era of antiviral prophylaxis and preemptive therapy. *Blood* 2004;103:2003-2008.
47. Maffini E, Giaccone L, Festuccia M et al. Treatment of CMV infection after allogeneic hematopoietic stem cell transplantation. *Expert.Rev.Hematol.* 2016;9:585-596.
48. Boeckh M, Kim HW, Flowers ME, Meyers JD, Bowden RA. Long-term acyclovir for prevention of varicella zoster virus disease after allogeneic hematopoietic cell transplantation--a randomized double-blind placebo-controlled study. *Blood* 2006;107:1800-1805.
49. Verhoeven DH, Claas EC, Jol-van der Zijde CM et al. Reactivation of Human Herpes Virus-6 After Pediatric Stem Cell Transplantation: Risk Factors, Onset, Clinical Symptoms and Association With Severity of Acute Graft-Versus-Host Disease. *Pediatr.Infect.Dis.J.* 2015;34:1118-1127.
50. Lenaerts L, De CE, Naessens L. Clinical features and treatment of adenovirus infections. *Rev.Med.Viro.* 2008;18:357-374.

51. Schilham MW, Claas EC, van ZW et al. High levels of adenovirus DNA in serum correlate with fatal outcome of adenovirus infection in children after allogeneic stem-cell transplantation. *Clin.Infect.Dis.* 2002;35:526-532.
52. Lankester AC, Heemskerk B, Claas EC et al. Effect of ribavirin on the plasma viral DNA load in patients with disseminating adenovirus infection. *Clin.Infect.Dis.* 2004;38:1521-1525.
53. Lalezari JP, Drew WL, Glutzer E et al. (S)-1-[3-hydroxy-2-(phosphonylmethoxy)propyl]cytosine (cidofovir): results of a phase I/II study of a novel antiviral nucleotide analogue. *J.Infect.Dis.* 1995;171:788-796.
54. Vandercam B, Moreau M, Goffin E et al. Cidofovir-induced end-stage renal failure. *Clin.Infect.Dis.* 1999;29:948-949.
55. Bhadri VA, Lee-Horn L, Shaw PJ. Safety and tolerability of cidofovir in high-risk pediatric patients. *Transpl.Infect.Dis.* 2009;11:373-379.
56. Ljungman P, Ribaud P, Eyrich M et al. Cidofovir for adenovirus infections after allogeneic hematopoietic stem cell transplantation: a survey by the Infectious Diseases Working Party of the European Group for Blood and Marrow Transplantation. *Bone Marrow Transplant.* 2003;31:481-486.
57. Robin M, Marque-Juillet S, Scieux C et al. Disseminated adenovirus infections after allogeneic hematopoietic stem cell transplantation: incidence, risk factors and outcome. *Haematologica* 2007;92:1254-1257.
58. Symeonidis N, Jakubowski A, Pierre-Louis S et al. Invasive adenoviral infections in T-cell-depleted allogeneic hematopoietic stem cell transplantation: high mortality in the era of cidofovir. *Transpl.Infect.Dis.* 2007;9:108-113.
59. Yusuf U, Hale GA, Carr J et al. Cidofovir for the treatment of adenoviral infection in pediatric hematopoietic stem cell transplant patients. *Transplantation* 2006;81:1398-1404.
60. Hiwarkar P, Amrolia P, Sivaprakasam P et al. Brincidofovir is highly efficacious in controlling adenoviremia in pediatric recipients of hematopoietic cell transplant. *Blood* 2017;129:2033-2037.
61. Florescu DF, Pergam SA, Neely MN et al. Safety and efficacy of CMX001 as salvage therapy for severe adenovirus infections in immunocompromised patients. *Biol.Blood Marrow Transplant.* 2012;18:731-738.
62. Bosch M, Khan FM, Storek J. Immune reconstitution after hematopoietic cell transplantation. *Curr.Opin.Hematol.* 2012;19:324-335.
63. Khan FM, Sy S, Louie P et al. Nasal epithelial cells of donor origin after allogeneic hematopoietic cell transplantation are generated at a faster rate in the first 3 months compared with later posttransplantation. *Biol.Blood Marrow Transplant* 2010;16:1658-1664.
64. Naughton MA, Botto M, Carter MJ et al. Extrahepatic secreted complement C3 contributes to circulating C3 levels in humans. *J.Immunol.* 1996;156:3051-3056.
65. Alper CA, Johnson AM, Birtch AG, Moore FD. Human C'3: evidence for the liver as the primary site of synthesis. *Science* 1969;163:286-288.
66. Auffermann-Gretzinger S, Lossos IS, Vayntrub TA et al. Rapid establishment of dendritic cell chimerism in allogeneic hematopoietic cell transplant recipients. *Blood* 2002;99:1442-1448.
67. Andani R, Robertson I, Macdonald KP et al. Origin of Langerhans cells in normal skin and chronic GVHD after hematopoietic stem-cell transplantation. *Exp.Dermatol.* 2014;23:75-77.
68. Klein L, Kyewski B, Allen PM, Hogquist KA. Positive and negative selection of the T cell repertoire: what thymocytes see (and don't see). *Nat.Rev.Immunol.* 2014;14:377-391.
69. Becattini S, Latorre D, Mele F et al. T cell immunity. Functional heterogeneity of human memory CD4(+) T cell clones primed by pathogens or vaccines. *Science* 2015;347:400-406.
70. Appay V, van Lier RA, Sallusto F, Roederer M. Phenotype and function of human T lymphocyte subsets: consensus and issues. *Cytometry A* 2008;73:975-983.
71. Weinberg K, Blazar BR, Wagner JE et al. Factors affecting thymic function after allogeneic hematopoietic stem cell transplantation. *Blood* 2001;97:1458-1466.
72. Eefting M, von dem Borne PA, de Wreede LC et al. Intentional donor lymphocyte-induced limited acute graft-versus-host disease is essential for long-term survival of relapsed acute myeloid leukemia after allogeneic stem cell transplantation. *Haematologica* 2014;99:751-758.
73. van Bergen CA, van Luxemburg-Heijls SA, de Wreede LC et al. Selective graft-versus-leukemia depends on magnitude and diversity of the alloreactive T cell response. *J.Clin.Invest* 2017;127:517-529.
74. Einsele H, Roosnek E, Rufer N et al. Infusion of cytomegalovirus (CMV)-specific T cells for the treatment of CMV infection not responding to antiviral chemotherapy. *Blood* 2002;99:3916-3922.

75. Rooney CM, Smith CA, Ng CY et al. Infusion of cytotoxic T cells for the prevention and treatment of Epstein-Barr virus-induced lymphoma in allogeneic transplant recipients. *Blood* 1998;92:1549-1555.
76. Peggs KS, Verfuerth S, Pizzey A et al. Adoptive cellular therapy for early cytomegalovirus infection after allogeneic stem-cell transplantation with virus-specific T-cell lines. *Lancet* 2003;362:1375-1377.
77. Cobbold M, Khan N, Pourghayehsari B et al. Adoptive transfer of cytomegalovirus-specific CTL to stem cell transplant patients after selection by HLA-peptide tetramers. *J.Exp.Med.* 2005;202:379-386.
78. Goepfert PA, Bansal A, Edwards BH et al. A significant number of human immunodeficiency virus epitope-specific cytotoxic T lymphocytes detected by tetramer binding do not produce gamma interferon. *J.Viro.* 2000;74:10249-10255.
79. De Rosa SC, Lu FX, Yu J et al. Vaccination in humans generates broad T cell cytokine responses. *J.Immunol.* 2004;173:5372-5380.
80. Feuchtinger T, Matthes-Martin S, Richard C et al. Safe adoptive transfer of virus-specific T-cell immunity for the treatment of systemic adenovirus infection after allogeneic stem cell transplantation. *Br.J.Haematol.* 2006;134:64-76.
81. Moosmann A, Bigalke I, Tischer J et al. Effective and long-term control of EBV PTLD after transfer of peptide-selected T cells. *Blood* 2010;115:2960-2970.
82. Mackinnon S, Thomson K, Verfuerth S, Peggs K, Lowdell M. Adoptive cellular therapy for cytomegalovirus infection following allogeneic stem cell transplantation using virus-specific T cells. *Blood Cells Mol.Dis.* 2008;40:63-67.
83. Leen AM, Bolland CM, Mendizabal AM et al. Multicenter study of banked third-party virus-specific T cells to treat severe viral infections after hematopoietic stem cell transplantation. *Blood* 2013;121:5113-5123.
84. Krebs P, Barnes MJ, Lampe K et al. NK-cell-mediated killing of target cells triggers robust antigen-specific T-cell-mediated and humoral responses. *Blood* 2009;113:6593-6602.
85. Martin-Fontech A, Thomsen LL, Brett S et al. Induced recruitment of NK cells to lymph nodes provides IFN-gamma for T(H)1 priming. *Nat.Immunol.* 2004;5:1260-1265.
86. Dokun AO, Kim S, Smith HR et al. Specific and nonspecific NK cell activation during virus infection. *Nat.Immunol.* 2001;2:951-956.
87. Vivier E, Raulet DH, Moretta A et al. Innate or adaptive immunity? The example of natural killer cells. *Science* 2011;331:44-49.
88. Artis D, Spits H. The biology of innate lymphoid cells. *Nature* 2015;517:293-301.
89. Serafini N, Vossenrich CA, Di Santo JP. Transcriptional regulation of innate lymphoid cell fate. *Nat.Rev.Immunol.* 2015;15:415-428.
90. Eissens DN, Spanholz J, van der Meer A et al. Defining early human NK cell developmental stages in primary and secondary lymphoid tissues. *PLoS.One.* 2012;7:e30930.
91. Freud AG, Yu J, Caligiuri MA. Human natural killer cell development in secondary lymphoid tissues. *Semin.Immunol.* 2014;26:132-137.
92. Freud AG, Becknell B, Roychowdhury S et al. A human CD34(+) subset resides in lymph nodes and differentiates into CD56bright natural killer cells. *Immunity*. 2005;22:295-304.
93. Freud AG, Yokohama A, Becknell B et al. Evidence for discrete stages of human natural killer cell differentiation in vivo. *J.Exp.Med.* 2006;203:1033-1043.
94. Hughes T, Briercheck EL, Freud AG et al. The transcription Factor AHR prevents the differentiation of a stage 3 innate lymphoid cell subset to natural killer cells. *Cell Rep.* 2014;8:150-162.
95. Montaldo E, Del Zotto G, Della Chiesa M. et al. Human NK cell receptors/markers: a tool to analyze NK cell development, subsets and function. *Cytometry A* 2013;83:702-713.
96. Melsen JE, Lugthart G, Lankester AC, Schilham MW. Human Circulating and Tissue-Resident CD56(bright) Natural Killer Cell Populations. *Front Immunol.* 2016;7:262.
97. Romagnani C, Juelke K, Falco M et al. CD56 bright CD16 - Killer Ig-Like Receptor - NK Cells display longer telomeres and acquire features of CD56 dim NK Cells upon activation. *J.Immunol.* 2007;178:4947-4955.
98. Matos ME, Schnier GS, Beecher MS et al. Expression of a functional c-kit receptor on a subset of natural killer cells. *J.Exp.Med.* 1993;178:1079-1084.
99. Bjorkstrom NK, Riese P, Heuts F et al. Expression patterns of NKG2A, KIR, and CD57 define a process of CD56dim NK-cell differentiation uncoupled from NK-cell education. *Blood* 2010;116:3853-3864.
100. Beziat V, Duffy D, Quoc SN et al. CD56brightCD16+ NK cells: a functional intermediate stage of NK cell differentiation. *J.Immunol.* 2011;186:6753-6761.

101. Fauriat C, Long EO, Ljunggren HG, Bryceson YT. Regulation of human NK-cell cytokine and chemokine production by target cell recognition. *Blood* 2010;115:2167-2176.
102. Anfossi N, Andre P, Guia S et al. Human NK cell education by inhibitory receptors for MHC class I. *Immunity*. 2006;25:331-342.
103. De Maria A., Bozzano F, Cantoni C, Moretta L. Revisiting human natural killer cell subset function revealed cytolytic CD56(dim)CD16+ NK cells as rapid producers of abundant IFN-gamma on activation. *Proc.Natl.Acad.Sci.U.S.A* 2011;108:728-732.
104. Cooper MA, Fehniger TA, Turner SC et al. Human natural killer cells: a unique innate immunoregulatory role for the CD56(bright) subset. *Blood* 2001;97:3146-3151.
105. Takahashi E, Kuranaga N, Satoh K et al. Induction of CD16+ CD56bright NK cells with antitumour cytotoxicity not only from CD16- CD56bright NK Cells but also from CD16- CD56dim NK cells. *Scand.J.Immunol.* 2007;65:126-138.
106. Westermann J, Pabst R. Distribution of lymphocyte subsets and natural killer cells in the human body. *Clin.Investig.* 1992;70:539-544.
107. Carrega P, Bonaccorsi I, Di Carlo E. et al. CD56(bright)perforin(low) noncytotoxic human NK cells are abundant in both healthy and neoplastic solid tissues and recirculate to secondary lymphoid organs via afferent lymph. *J.Immunol.* 2014;192:3805-3815.
108. Fehniger TA, Cooper MA, Nuovo GJ et al. CD56bright natural killer cells are present in human lymph nodes and are activated by T cell-derived IL-2: a potential new link between adaptive and innate immunity. *Blood* 2003;101:3052-3057.
109. Lanier LL. Up on the tightrope: natural killer cell activation and inhibition. *Nat.Immunol.* 2008;9:495-502.
110. Newman KC, Riley EM. Whatever turns you on: accessory-cell-dependent activation of NK cells by pathogens. *Nat.Rev.Immunol.* 2007;7:279-291.
111. Hoglund P, Brodin P. Current perspectives of natural killer cell education by MHC class I molecules. *Nat.Rev.Immunol.* 2010;10:724-734.
112. Cooley S, Xiao F, Pitt M et al. A subpopulation of human peripheral blood NK cells that lacks inhibitory receptors for self-MHC is developmentally immature. *Blood* 2007;110:578-586.
113. Parham P, Moffett A. Variable NK cell receptors and their MHC class I ligands in immunity, reproduction and human evolution. *Nat.Rev.Immunol.* 2013;13:133-144.
114. Pak-Wittel MA, Yang L, Sojka DK, Rivenbark JG, Yokoyama WM. Interferon-gamma mediates chemokine-dependent recruitment of natural killer cells during viral infection. *Proc.Natl.Acad.Sci.U.S.A* 2013;110:E50-E59.
115. Crome SQ, Lang PA, Lang KS, Ohashi PS. Natural killer cells regulate diverse T cell responses. *Trends Immunol.* 2013;34:342-349.
116. Bancroft GJ, Shellam GR, Chalmer JE. Genetic influences on the augmentation of natural killer (NK) cells during murine cytomegalovirus infection: correlation with patterns of resistance. *J.Immunol.* 1981;126:988-994.
117. Biron CA, Byron KS, Sullivan JL. Severe herpesvirus infections in an adolescent without natural killer cells. *N Engl.J.Med.* 1989;320:1731-1735.
118. Orange JS. Natural killer cell deficiency. *J.Allergy Clin.Immunol.* 2013;132:515-525.
119. Della CM, Muccio L, Moretta A. CMV induces rapid NK cell maturation in HSCT recipients. *Immunol.Lett.* 2013;155:11-13.
120. Williams H, McAulay K, Macsween KF et al. The immune response to primary EBV infection: a role for natural killer cells. *Br.J.Haematol.* 2005;129:266-274.
121. Azzi T, Lunemann A, Murer A et al. Role for early-differentiated natural killer cells in infectious mononucleosis. *Blood* 2014;124:2533-2543.
122. Ruggeri L, Capanni M, Urbani E et al. Effectiveness of donor natural killer cell alloreactivity in mismatched hematopoietic transplants. *Science* 2002;295:2097-2100.
123. Miller JS, Soignier Y, Panoskaltsis-Mortari A et al. Successful adoptive transfer and in vivo expansion of human haploididential NK cells in patients with cancer. *Blood* 2005;105:3051-3057.
124. Locatelli F, Moretta F, Brescia L, Merli P. Natural killer cells in the treatment of high-risk acute leukaemia. *Semin.Immunol.* 2014;26:173-179.
125. Bosch M, Dhadda M, Hoegh-Petersen M et al. Immune reconstitution after anti-thymocyte globulin-conditioned hematopoietic cell transplantation. *Cyotherapy*. 2012;14:1258-1275.

126. Dulphy N, Haas P, Busson M et al. An unusual CD56(bright) CD16(low) NK cell subset dominates the early posttransplant period following HLA-matched hematopoietic stem cell transplantation. *J.Immunol.* 2008;181:2227-2237.
127. Vukicevic M, Chalandron Y, Helg C et al. CD56bright NK cells after hematopoietic stem cell transplantation are activated mature NK cells that expand in patients with low numbers of T cells. *Eur.J.Immunol.* 2010;40:3246-3254.
128. Silva A, Andrews DM, Brooks AG, Smyth MJ, Hayakawa Y. Application of CD27 as a marker for distinguishing human NK cell subsets. *Int.Immunol.* 2008;20:625-630.
129. Foley B, Cooley S, Verneris MR et al. Cytomegalovirus reactivation after allogeneic transplantation promotes a lasting increase in educated NKG2C⁺ natural killer cells with potent function. *Blood* 2011
130. Foley B, Cooley S, Verneris MR et al. NK cell education after allogeneic transplantation: dissociation between recovery of cytokine-producing and cytotoxic functions. *Blood* 2011;118:2784-2792.
131. Pical-Izard C, Crocchiolo R, Grangeaud S et al. Reconstitution of natural killer cells in HLA-matched HSCT after reduced-intensity conditioning: impact on clinical outcome. *Biol.Blood Marrow Transplant* 2015;21:429-439.
132. Simonetta F, Pradier A, Bosshard C et al. NK Cell Functional Impairment after Allogeneic Hematopoietic Stem Cell Transplantation Is Associated with Reduced Levels of T-bet and Eomesodermin. *J.Immunol.* 2015;195:4712-4720.
133. Bjorklund AT, Schaffer M, Fauriat C et al. NK cells expressing inhibitory KIR for non-self-ligands remain tolerant in HLA-matched sibling stem cell transplantation. *Blood* 2010;115:2686-2694.
134. Nguyen S, Kuentz M, Vernant JP et al. Involvement of mature donor T cells in the NK cell reconstitution after haploidentical hematopoietic stem-cell transplantation. *Leukemia* 2008;22:344-352.
135. Vago L, Forno B, Sormani MP et al. Temporal, quantitative, and functional characteristics of single-KIR-positive alloreactive natural killer cell recovery account for impaired graft-versus-leukemia activity after haploidentical hematopoietic stem cell transplantation. *Blood* 2008;112:3488-3499.
136. Nguyen S, Dhedin N, Vernant JP et al. NK-cell reconstitution after haploidentical hematopoietic stem-cell transplantsations: immaturity of NK cells and inhibitory effect of NKG2A override GvL effect. *Blood* 2005;105:4135-4142.
137. Nguyen S, Beziat V, Dhedin N et al. HLA-E upregulation on IFN-gamma-activated AML blasts impairs CD94/NKG2A-dependent NK cytolysis after haplo-mismatched hematopoietic SCT. *Bone Marrow Transplant* 2009;43:693-699.
138. Ghasemzadeh M, Hosseini E, Schwarer AP, Pourfathollah AA. NK cell maturation to CD56(dim) subset associated with high levels of NCRs overrides the inhibitory effect of NKG2A and recovers impaired NK cell cytolytic potential after allogeneic hematopoietic stem cell transplantation. *Leuk.Res.* 2016;43:58-65.
139. Sinclair J. Human cytomegalovirus: Latency and reactivation in the myeloid lineage. *J.Clin.Virol.* 2008;41:180-185.
140. Hebart H, Einsele H. Clinical aspects of CMV infection after stem cell transplantation. *Hum.Immunol.* 2004;65:432-436.
141. Li CR, Greenberg PD, Gilbert MJ, Goodrich JM, Riddell SR. Recovery of HLA-restricted cytomegalovirus (CMV)-specific T-cell responses after allogeneic bone marrow transplant: correlation with CMV disease and effect of ganciclovir prophylaxis. *Blood* 1994;83:1971-1979.
142. Barron MA, Gao D, Springer KL et al. Relationship of reconstituted adaptive and innate cytomegalovirus (CMV)-specific immune responses with CMV viremia in hematopoietic stem cell transplant recipients. *Clin.Infect.Dis.* 2009;49:1777-1783.
143. Williams KM, Hakim FT, Gress RE. T cell immune reconstitution following lymphodepletion. *Semin.Immunol.* 2007;19:318-330.
144. Tchao NK, Turka LA. Lymphodepletion and homeostatic proliferation: implications for transplantation. *Am.J.Transplant.* 2012;12:1079-1090.
145. Romero P, Zappelius A, Kurth I et al. Four functionally distinct populations of human effector-memory CD8+ T lymphocytes. *J.Immunol.* 2007;178:4112-4119.
146. Appay V, Dunbar PR, Callan M et al. Memory CD8+ T cells vary in differentiation phenotype in different persistent virus infections. *Nat.Med.* 2002;8:379-385.
147. Gamadia LE, Rentenaar RJ, Baars PA et al. Differentiation of cytomegalovirus-specific CD8(+) T cells in healthy and immunosuppressed virus carriers. *Blood* 2001;98:754-761.
148. Looney RJ, Falsey A, Campbell D et al. Role of cytomegalovirus in the T cell changes seen in elderly individuals. *Clin.Immunol.* 1999;90:213-219.

149. Marchant A, Appay V, Van Der Sande M et al. Mature CD8(+) T lymphocyte response to viral infection during fetal life. *J.Clin.Invest.* 2003;111:1747-1755.
150. Kuijpers TW, Vossen MT, Gent MR et al. Frequencies of circulating cytolytic, CD45RA+CD27-, CD8+ T lymphocytes depend on infection with CMV. *J.Immunol.* 2003;170:4342-4348.
151. Miles DJ, van der Sande M, Jeffries D et al. Cytomegalovirus infection in Gambian infants leads to profound CD8 T-cell differentiation. *J.Viro.* 2007;81:5766-5776.
152. Miles DJ, van der Sande M, Jeffries D et al. Maintenance of large subpopulations of differentiated CD8 T-cells two years after cytomegalovirus infection in Gambian infants. *PLoS.One.* 2008;3:e2905.
153. van de Berg PJ, van SA, ten Berge IJ, van Lier RA. A fingerprint left by cytomegalovirus infection in the human T cell compartment. *J.Clin.Viro.* 2008;41:213-217.
154. Cantisani S, Torre-Cisneros J, Lara R et al. Age-dependent association between low frequency of CD27/CD28 expression on pp65 CD8+ T cells and cytomegalovirus replication after transplantation. *Clin.Vaccine Immunol.* 2009;16:1429-1438.
155. Peggs KS, Verfuerth S, Pizzey A et al. Reconstitution of T-cell repertoire after autologous stem cell transplantation: influence of CD34 selection and cytomegalovirus infection. *Biol.Blood Marrow Transplant.* 2003;9:198-205.
156. Luo XH, Huang XJ, Li D et al. Immune reconstitution to cytomegalovirus following partially matched-related donor transplantation: impact of in vivo T-cell depletion and granulocyte colony-stimulating factor-primed peripheral blood/bone marrow mixed grafts. *Transpl.Infect.Dis.* 2013;15:22-33.
157. Wursch AM, Gratama JW, Middeldorp JM et al. The effect of cytomegalovirus infection on T lymphocytes after allogeneic bone marrow transplantation. *Clin.Exp.Immunol.* 1985;62:278-287.
158. Niesters HG, van Esser J, Fries E et al. Development of a real-time quantitative assay for detection of Epstein-Barr virus. *J.Clin.Microbiol.* 2000;38:712-715.
159. Claas EC, Schilham MW, de Brouwer CS et al. Internally controlled real-time PCR monitoring of adenovirus DNA load in serum or plasma of transplant recipients. *J.Clin.Microbiol.* 2005;43:1738-1744.
160. Kalpoe JS, Kroes AC, de Jong MD et al. Validation of clinical application of cytomegalovirus plasma DNA load measurement and definition of treatment criteria by analysis of correlation to antigen detection. *J.Clin.Microbiol.* 2004;42:1498-1504.
161. Boeckh M, Ljungman P. How we treat cytomegalovirus in hematopoietic cell transplant recipients. *Blood* 2009;113:5711-5719.
162. Meijer E, Cornelissen JJ. Epstein-Barr virus-associated lymphoproliferative disease after allogeneic haematopoietic stem cell transplantation: molecular monitoring and early treatment of high-risk patients. *Curr.Opin.Hematol.* 2008;15:576-585.
163. van Tol MJ, Claas EC, Heemskerk B et al. Adenovirus infection in children after allogeneic stem cell transplantation: diagnosis, treatment and immunity. *Bone Marrow Transplant.* 2005;35 Suppl 1:S73-S76.
164. Shaulov A, Murali-Krishna K. CD8 T cell expansion and memory differentiation are facilitated by simultaneous and sustained exposure to antigenic and inflammatory milieu. *J.Immunol.* 2008;180:1131-1138.
165. Gamadia LE, van Leeuwen EM, Remmerswaal EB et al. The size and phenotype of virus-specific T cell populations is determined by repetitive antigenic stimulation and environmental cytokines. *J.Immunol.* 2004;172:6107-6114.
166. van Leeuwen EM, Koning JJ, Remmerswaal EB et al. Differential usage of cellular niches by cytomegalovirus versus EBV- and influenza virus-specific CD8+ T cells. *J.Immunol.* 2006;177:4998-5005.
167. Wherry EJ. T cell exhaustion. *Nat.Immunol.* 2011;12:492-499.
168. Cicin-Sain L, Sylwester AW, Hagen SI et al. Cytomegalovirus-specific T cell immunity is maintained in immunosenescent rhesus macaques. *J.Immunol.* 2011;187:1722-1732.
169. Day CL, Kaufmann DE, Kiepiela P et al. PD-1 expression on HIV-specific T cells is associated with T-cell exhaustion and disease progression. *Nature* 2006;443:350-354.
170. Hertoghs KM, Moerland PD, van SA et al. Molecular profiling of cytomegalovirus-induced human CD8+ T cell differentiation. *J.Clin.Invest.* 2010;120:4077-4090.
171. Matloubian M, Concepcion RJ, Ahmed R. CD4+ T cells are required to sustain CD8+ cytotoxic T-cell responses during chronic viral infection. *J.Viro.* 1994;68:8056-8063.
172. Walter EA, Greenberg PD, Gilbert MJ et al. Reconstitution of cellular immunity against cytomegalovirus in recipients of allogeneic bone marrow by transfer of T-cell clones from the donor. *N Engl.J.Med.* 1995;333:1038-1044.

173. van Leeuwen EM, Remmerswaal EB, Heemskerk MH, ten Berge IJ, van Lier RA. Strong selection of virus-specific cytotoxic CD4+ T-cell clones during primary human cytomegalovirus infection. *Blood* 2006;108:3121-3127.
174. Dechanet J, Merville P, Lim A et al. Implication of gammadelta T cells in the human immune response to cytomegalovirus. *J.Clin.Invest* 1999;103:1437-1449.
175. Lafarge X, Merville P, Cazin MC et al. Cytomegalovirus infection in transplant recipients resolves when circulating gammadelta T lymphocytes expand, suggesting a protective antiviral role. *J.Infect.Dis.* 2001;184:533-541.
176. Remmerswaal EB, Havenith SH, Idu MM et al. Human virus-specific effector-type T cells accumulate in blood but not in lymph nodes. *Blood* 2012;119:1702-1712.
177. Klarenbeek PL, Remmerswaal EB, ten Berge IJ et al. Deep sequencing of antiviral T-cell responses to HCMV and EBV in humans reveals a stable repertoire that is maintained for many years. *PLoS.Pathog.* 2012;8:e1002889.
178. Elmaagaci AH, Steckel NK, Koldehoff M et al. Early human cytomegalovirus replication after transplantation is associated with a decreased relapse risk: evidence for a putative virus-versus-leukemia effect in acute myeloid leukemia patients. *Blood* 2011;118:1402-1412.
179. Gustafsson A, Levitsky V, Zou JZ et al. Epstein-Barr virus (EBV) load in bone marrow transplant recipients at risk to develop posttransplant lymphoproliferative disease: prophylactic infusion of EBV-specific cytotoxic T cells. *Blood* 2000;95:807-814.
180. Leen AM, Myers GD, Sili U et al. Monoculture-derived T lymphocytes specific for multiple viruses expand and produce clinically relevant effects in immunocompromised individuals. *Nat.Med.* 2006;12:1160-1166.
181. Leen AM, Christin A, Myers GD et al. Cytotoxic T lymphocyte therapy with donor T cells prevents and treats adenovirus and Epstein-Barr virus infections after haploidentical and matched unrelated stem cell transplantation. *Blood* 2009;114:4283-4292.
182. Fujita Y, Leen AM, Sun J et al. Exploiting cytokine secretion to rapidly produce multivirus-specific T cells for adoptive immunotherapy. *J.Immunother.* 2008;31:665-674.
183. Gerdemann U, Christin AS, Vera JF et al. Nucleofection of DCs to generate Multivirus-specific T cells for prevention or treatment of viral infections in the immunocompromised host. *Mol.Ther.* 2009;17:1616-1625.
184. Zandvliet ML, Falkenburg JH, van LE et al. Combined CD8+ and CD4+ adenovirus hexon-specific T cells associated with viral clearance after stem cell transplantation as treatment for adenovirus infection. *Haematologica* 2010
185. Rickinson AB, Lee SP, Steven NM. Cytotoxic T lymphocyte responses to Epstein-Barr virus. *Curr.Opin.Immunol.* 1996;8:492-497.
186. Wills MR, Carmichael AJ, Mynard K et al. The human cytotoxic T-lymphocyte (CTL) response to cytomegalovirus is dominated by structural protein pp65: frequency, specificity, and T-cell receptor usage of pp65-specific CTL. *J.Viro.* 1996;70:7569-7579.
187. Zandvliet ML, van LE, Jedema I et al. Co-ordinated isolation of CD8(+) and CD4(+) T cells recognizing a broad repertoire of cytomegalovirus pp65 and IE1 epitopes for highly specific adoptive immunotherapy. *Cytotherapy*. 2010
188. Savoldo B, Cubbage ML, Durett AG et al. Generation of EBV-specific CD4+ cytotoxic T cells from virus naive individuals. *J.Immunol.* 2002;168:909-918.
189. Altman JD, Moss PA, Goulder PJ et al. Phenotypic analysis of antigen-specific T lymphocytes. *Science* 1996;274:94-96.
190. Karlsson H, Brewin J, Kinnon C, Veys P, Amrolia PJ. Generation of trispecific cytotoxic T cells recognizing cytomegalovirus, adenovirus, and Epstein-Barr virus: an approach for adoptive immunotherapy of multiple pathogens. *J.Immunother.* 2007;30:544-556.
191. Zandvliet ML, Falkenburg JH, Jedema I et al. Detailed analysis of IFNg response upon activation permits efficient isolation of cytomegalovirus-specific CD8+ T cells for adoptive immunotherapy. *J.Immunother.* 2009;32:513-523.
192. Flomenberg P, Piaskowski V, Truitt RL, Casper JT. Characterization of human proliferative T cell responses to adenovirus. *J.Infect.Dis.* 1995;171:1090-1096.
193. Walter EA, Greenberg PD, Gilbert MJ et al. Reconstitution of cellular immunity against cytomegalovirus in recipients of allogeneic bone marrow by transfer of T-cell clones from the donor. *N Engl.J.Med.* 1995;333:1038-1044.

194. Melenhorst JJ, Leen AM, Bolland CM et al. Allogeneic virus-specific T cells with HLA alloreactivity do not produce GVHD in human subjects. *Blood* 2010
195. Dazzi F, Szydlo RM, Craddock C et al. Comparison of single-dose and escalating-dose regimens of donor lymphocyte infusion for relapse after allografting for chronic myeloid leukemia. *Blood* 2000;95:67-71.
196. Sakaguchi S. Naturally arising CD4+ regulatory t cells for immunologic self-tolerance and negative control of immune responses. *Annu.Rev.Immunol.* 2004;22:531-562.
197. Wang J, Ioan-Facsinay A, van der Voort EI, Huizinga TW, Toes RE. Transient expression of FOXP3 in human activated nonregulatory CD4+ T cells. *Eur.J.Immunol.* 2007;37:129-138.
198. Hoffmann P, Ermann J, Edinger M, Fathman CG, Strober S. Donor-type CD4(+)CD25(+) regulatory T cells suppress lethal acute graft-versus-host disease after allogeneic bone marrow transplantation. *J.Exp.Med.* 2002;196:389-399.
199. Taylor PA, Lees CJ, Blazzer BR. The infusion of ex vivo activated and expanded CD4(+)CD25(+) immune regulatory cells inhibits graft-versus-host disease lethality. *Blood* 2002;99:3493-3499.
200. Brunstein CG, Miller JS, Cao Q et al. Infusion of ex vivo expanded T regulatory cells in adults transplanted with umbilical cord blood: safety profile and detection kinetics. *Blood* 2010
201. Di IM, Falzetti F, Carotti A et al. Tregs prevent GVHD and promote immune reconstitution in HLA-haploididentical transplantation. *Blood* 2011;117:3921-3928.
202. Thornton AM, Shevach EM. Suppressor effector function of CD4+CD25+ immunoregulatory T cells is antigen nonspecific. *J.Immunol.* 2000;164:183-190.
203. Nguyen VH, Shashidhar S, Chang DS et al. The impact of regulatory T cells on T-cell immunity following hematopoietic cell transplantation. *Blood* 2008;111:945-953.
204. Leen AM, Sili U, Vanin EF et al. Conserved CTL epitopes on the adenovirus hexon protein expand subgroup cross-reactive and subgroup-specific CD8+ T cells. *Blood* 2004;104:2432-2440.
205. Zandvliet ML, Falkenburg JH, van LE et al. Combined CD8+ and CD4+ adenovirus hexon-specific T cells associated with viral clearance after stem cell transplantation as treatment for adenovirus infection. *Haematologica* 2010;95:1943-1951.
206. Howard DS, Phillips II GL, Reece DE et al. Adenovirus infections in hematopoietic stem cell transplant recipients. *Clin.Infect.Dis.* 1999;29:1494-1501.
207. Chakrabarti S, Mautner V, Osman H et al. Adenovirus infections following allogeneic stem cell transplantation: incidence and outcome in relation to graft manipulation, immunosuppression, and immune recovery. *Blood* 2002;100:1619-1627.
208. Walls T, Shankar AG, Shingadia D. Adenovirus: an increasingly important pathogen in paediatric bone marrow transplant patients. *Lancet Infect.Dis.* 2003;3:79-86.
209. Feuchtinger T, Matthes-Martin S, Richard C et al. Safe adoptive transfer of virus-specific T-cell immunity for the treatment of systemic adenovirus infection after allogeneic stem cell transplantation. *Br.J.Haematol.* 2006;134:64-76.
210. Morfin F, Dupuis-Girod S, Frobert E et al. Differential susceptibility of adenovirus clinical isolates to cidofovir and ribavirin is not related to species alone. *Antivir.Ther.* 2009;14:55-61.
211. Naesens L, Lenaerts L, Andrei G et al. Antiadenovirus activities of several classes of nucleoside and nucleotide analogues. *Antimicrob.Agents Chemother.* 2005;49:1010-1016.
212. Morfin F, Dupuis-Girod S, Mundweiler S et al. In vitro susceptibility of adenovirus to antiviral drugs is species-dependent. *Antivir.Ther.* 2005;10:225-229.
213. Muller WJ, Levin MJ, Shin YK et al. Clinical and in vitro evaluation of cidofovir for treatment of adenovirus infection in pediatric hematopoietic stem cell transplant recipients. *Clin.Infect.Dis.* 2005;41:1812-1816.
214. Hoffman JA, Shah AJ, Ross LA, Kapoor N. Adenoviral infections and a prospective trial of cidofovir in pediatric hematopoietic stem cell transplantation. *Biol.Blood Marrow Transplant.* 2001;7:388-394.
215. Mynarek M, Ganzenmueller T, Mueller-Heine A et al. Patient, virus and treatment-related risk factors in pediatric adenovirus infection after stem cell transplantation: results of a routine monitoring program. *Biol.Blood Marrow Transplant.* 2013
216. Jacobs R, Stoll M, Stratmann G et al. CD16- CD56+ natural killer cells after bone marrow transplantation. *Blood* 1992;79:3239-3244.
217. Storek J, Dawson MA, Storer B et al. Immune reconstitution after allogeneic marrow transplantation compared with blood stem cell transplantation. *Blood* 2001;97:3380-3389.
218. Jost S, Altfeld M. Control of human viral infections by natural killer cells. *Annu.Rev.Immunol.* 2013;31:163-194.

219. Lanier LL. Evolutionary struggles between NK cells and viruses. *Nat.Rev.Immunol.* 2008;8:259-268.
220. Biron CA, Nguyen KB, Pien GC, Cousens LP, Salazar-Mather TP. Natural killer cells in antiviral defense: function and regulation by innate cytokines. *Annu.Rev.Immunol.* 1999;17:189-220.
221. Pahl JH, Verhoeven DH, Kwappenberg KM et al. Adenovirus type 35, but not type 5, stimulates NK cell activation via plasmacytoid dendritic cells and TLR9 signaling. *Mol.Immunol.* 2012;51:91-100.
222. Miller G, Lahrs S, Pillarisetty VG, Shah AB, DeMatteo RP. Adenovirus infection enhances dendritic cell immunostimulatory properties and induces natural killer and T-cell-mediated tumor protection. *Cancer Res.* 2002;62:5260-5266.
223. Routes JM. IFN increases class I MHC antigen expression on adenovirus-infected human cells without inducing resistance to natural killer cell killing. *J.Immunol.* 1992;149:2372-2377.
224. Walls T, Hawrami K, Ushiro-Lumb I et al. Adenovirus infection after pediatric bone marrow transplantation: is treatment always necessary? *Clin.Infect.Dis.* 2005;40:1244-1249.
225. La Rosa AM, Champlin RE, Mirza N et al. Adenovirus infections in adult recipients of blood and marrow transplants. *Clin.Infect.Dis.* 2001;32:871-876.
226. Ozdemir E, St John LS, Gillespie G et al. Cytomegalovirus reactivation following allogeneic stem cell transplantation is associated with the presence of dysfunctional antigen-specific CD8+ T cells. *Blood* 2002;100:3690-3697.
227. Gordon YJ, Araullo-Cruz TP, Johnson YF, Romanowski EG, Kinchington PR. Isolation of human adenovirus type 5 variants resistant to the antiviral cidofovir. *Invest Ophthalmol Vis Sci.* 1996;37:2774-2778.
228. Ljungman P. Would monitoring CMV immune responses allow improved control of CMV in stem cell transplant patients. *J.Clin.Virol.* 2006;35:493-495.
229. Solano C, Benet I, Remigia MJ et al. Immunological monitoring for guidance of preemptive antiviral therapy for active cytomegalovirus infection in allogeneic stem-cell transplant recipients: a pilot experience. *Transplantation* 2011;92:e17-e20.
230. Hauser A, Schrattbauer K, Najdanovic D et al. Optimized quantification of lymphocyte subsets by use of CD7 and CD33. *Cytometry A* 2013;83:316-323.
231. Lutz CT, Karapetyan A, Al-Attar A et al. Human NK cells proliferate and die in vivo more rapidly than T cells in healthy young and elderly adults. *J.Immunol.* 2011;186:4590-4598.
232. Kaplan J, Nolan D, Reed A. Altered lymphocyte markers and blastogenic responses associated with 24 hour delay in processing of blood samples. *J.Immunol.Methods* 1982;50:187-191.
233. Olson WC, Smolkin ME, Farris EM et al. Shipping blood to a central laboratory in multicenter clinical trials: effect of ambient temperature on specimen temperature, and effects of temperature on mononuclear cell yield, viability and immunologic function. *J.Transl.Med.* 2011;9:26.
234. Dobbs K, Notarangelo LD. 2016 CIS Annual Meeting Abstract 4514: NK cells from patients with RAG and ARTEMIS deficiency have an immature phenotype and display increased degranulation capacity - implications for hematopoietic stem cell transplantation. *J.Clin.Immunol.* 2016;36:283-284.
235. Dobbs K, Tabellini G, Calzoni E et al. Natural Killer Cells from Patients with Recombinase-Activating Gene and Non-Homologous End Joining Gene Defects Comprise a Higher Frequency of CD56bright NKG2A+++ Cells, and Yet Display Increased Degranulation and Higher Perforin Content. *Front Immunol.* 2017;8:798.
236. Hong HS, Ahmad F, Eberhard JM et al. Loss of CCR7 expression on CD56(bright) NK cells is associated with a CD56(dim)CD16(+) NK cell-like phenotype and correlates with HIV viral load. *PLoS.One.* 2012;7:e44820.
237. Lughart G, van Ostaijen-ten Dam MM, van Tol MJ, Lankester AC, Schilham MW. CD56(dim)CD16(-) NK cell phenotype can be induced by cryopreservation. *Blood* 2015;125:1842-1843.
238. van der Maaten LJ, Hinton GE. Visualizing High-Dimensional Data Using t-SNE. *Journal of Machine Learning Research* 2008;15:2579-2605.
239. van der Maaten LJ. Accelerating t-SNE using Tree-Based Algorithms. *Journal of Machine Learning Research* 2014;15:3221-3245.
240. Krijthe JH, van der Maaten LJ. Rtsne: T-Distributed Stochastic Neighbor Embedding using a Barnes-Hut Implementation. <https://CRAN.R-project.org/package=Rtsne> 2015;v0.11:
241. Bjorklund AK, Forkel M, Picelli S et al. The heterogeneity of human CD127(+) innate lymphoid cells revealed by single-cell RNA sequencing. *Nat.Immunol.* 2016;17:451-460.
242. Pahl JH, Ruslan SE, Buddingh EP et al. Anti-EGFR antibody cetuximab enhances the cytolytic activity of natural killer cells toward osteosarcoma. *Clin.Cancer Res.* 2012;18:432-441.

243. Lughart G, Melsen JE, Vervat C et al. Human Lymphoid Tissues Harbor a Distinct CD69+CXCR6+ NK Cell Population. *J.Immunol.* 2016;197:78-84.
244. Heemskerk B, van Vreeswijk T., Veltrop-Duits LA et al. Adenovirus-specific CD4+ T cell clones recognizing endogenous antigen inhibit viral replication in vitro through cognate interaction. *J.Immunol.* 2006;177:8851-8859.
245. Wickham H, Francois R. dplyr: A Grammar of Data Manipulation. <https://CRAN.R-project.org/package=dplyr> 2016;v0.5.0:
246. Zhao S, Guo Y, Sheng Q, Shyr Y. heatmap3: An Improved Heatmap Package. <https://CRAN.R-project.org/package=heatmap3> 2015;v1.1.1:
247. Wickham H, Chang W. ggplot2: Create Elegant Data Visualisations Using the Grammar of Graphics. <https://CRAN.R-project.org/package=ggplot2> 2016;v2.2.1:
248. Neuwirth E. RColorBrewer: ColorBrewer Palettes. <https://CRAN.R-project.org/package=RColorBrewer> 2014;v1.1-2:
249. Heinze G, Ploner M, Dunkler D, Southworth H. logistf: Firth's Bias-Reduced Logistic Regression. <https://CRAN.R-project.org/package=logistf> 2013;v1.22:
250. Holm S. A simple sequentially rejective multiple test procedure. *Scandinavian Journal of Statistics* 1979;6:65-70.
251. Scharton TM, Scott P. Natural killer cells are a source of interferon gamma that drives differentiation of CD4+ T cell subsets and induces early resistance to Leishmania major in mice. *J.Exp.Med.* 1993;178:567-577.
252. Gerosa F, Baldani-Guerra B, Nisii C et al. Reciprocal activating interaction between natural killer cells and dendritic cells. *J.Exp.Med.* 2002;195:327-333.
253. Askenase MH, Han SJ, Byrd AL et al. Bone-Marrow-Resident NK Cells Prime Monocytes for Regulatory Function during Infection. *Immunity*. 2015;42:1130-1142.
254. Vivier E, Raulet DH, Moretta A et al. Innate or adaptive immunity? The example of natural killer cells. *Science* 2011;331:44-49.
255. Westermann J, Pabst R. Distribution of lymphocyte subsets and natural killer cells in the human body. *Clin.Investig.* 1992;70:539-544.
256. Ferlazzo G, Pack M, Thomas D et al. Distinct roles of IL-12 and IL-15 in human natural killer cell activation by dendritic cells from secondary lymphoid organs. *Proc.Natl.Acad.Sci.U.S.A* 2004;101:16606-16611.
257. Tomasello E, Yessaad N, Gregoire E et al. Mapping of NKp46(+) Cells in Healthy Human Lymphoid and Non-Lymphoid Tissues. *Front Immunol.* 2012;3:344.
258. Gregoire C, Chasson L, Luci C et al. The trafficking of natural killer cells. *Immunol.Rev.* 2007;220:169-182.
259. Hazenberg MD, Spits H. Human innate lymphoid cells. *Blood* 2014;124:700-709.
260. Saeed AI, Sharov V, White J et al. TM4: a free, open-source system for microarray data management and analysis. *Biotechniques* 2003;34:374-378.
261. Marquardt N, Beziat V, Nystrom S et al. Cutting edge: identification and characterization of human intrahepatic CD49a+ NK cells. *J.Immunol.* 2015;194:2467-2471.
262. Ferlazzo G, Thomas D, Lin SL et al. The abundant NK cells in human secondary lymphoid tissues require activation to express killer cell Ig-like receptors and become cytolytic. *J.Immunol.* 2004;172:1455-1462.
263. Celli M, Fuchs A, Vermi W et al. A human natural killer cell subset provides an innate source of IL-22 for mucosal immunity. *Nature* 2009;457:722-725.
264. Cosulich ME, Rubartelli A, Rizzo A, Cozzolino F, Bargellesi A. Functional characterization of an antigen involved in an early step of T-cell activation. *Proc.Natl.Acad.Sci.U.S.A* 1987;84:4205-4209.
265. Hara T, Jung LK, Bjorndahl JM, Fu SM. Human T cell activation. III. Rapid induction of a phosphorylated 28 kD/32 kD disulfide-linked early activation antigen (EA 1) by 12-o-tetradecanoyl phorbol-13-acetate, mitogens, and antigens. *J.Exp.Med.* 1986;164:1988-2005.
266. Lopez-Cabrera M, Santis AG, Fernandez-Ruiz E et al. Molecular cloning, expression, and chromosomal localization of the human earliest lymphocyte activation antigen AIM/CD69, a new member of the C-type animal lectin superfamily of signal-transmitting receptors. *J.Exp.Med.* 1993;178:537-547.
267. Cyster JG, Schwab SR. Sphingosine-1-phosphate and lymphocyte egress from lymphoid organs. *Annu.Rev.Immunol.* 2012;30:69-94.
268. Shiow LR, Rosen DB, Brdickova N et al. CD69 acts downstream of interferon-alpha/beta to inhibit S1P1 and lymphocyte egress from lymphoid organs. *Nature* 2006;440:540-544.

269. Geissmann F, Cameron TO, Sidobre S et al. Intravascular immune surveillance by CXCR6+ NKT cells patrolling liver sinusoids. *PLoS.Biol.* 2005;3:e113.
270. Palendira U, Chinn R, Raza W et al. Selective accumulation of virus-specific CD8+ T cells with unique homing phenotype within the human bone marrow. *Blood* 2008;112:3293-3302.
271. Hudspeth K, Donadon M, Cimino M et al. Human liver-resident CD56/CD16 NK cells are retained within hepatic sinusoids via the engagement of CCR5 and CXCR6 pathways. *J.Autoimmun.* 2015;66:40-50.
272. Peng H, Jiang X, Chen Y et al. Liver-resident NK cells confer adaptive immunity in skin-contact inflammation. *J.Clin.Invest* 2013;123:1444-1456.
273. Paust S, Gill HS, Wang BZ et al. Critical role for the chemokine receptor CXCR6 in NK cell-mediated antigen-specific memory of haptens and viruses. *Nat.Immunol.* 2010;11:1127-1135.
274. Shibuya A, Campbell D, Hannum C et al. DNAM-1, a novel adhesion molecule involved in the cytolytic function of T lymphocytes. *Immunity*. 1996;4:573-581.
275. Enqvist M, Ask EH, Forslund E et al. Coordinated expression of DNAM-1 and LFA-1 in educated NK cells. *J.Immunol.* 2015;194:4518-4527.
276. Martinet L, Ferrari de Andrade L., Guillerey C et al. DNAM-1 expression marks an alternative program of NK cell maturation. *Cell Rep.* 2015;11:85-97.
277. Zhang Z, Wu N, Lu Y et al. DNAM-1 controls NK cell activation via an ITT-like motif. *J.Exp.Med.* 2015;212:2165-2182.
278. Carlsten M, Baumann BC, Simonsson M et al. Reduced DNAM-1 expression on bone marrow NK cells associated with impaired killing of CD34+ blasts in myelodysplastic syndrome. *Leukemia* 2010;24:1607-1616.
279. Vossen MT, Matmati M, Hertoghs KM et al. CD27 defines phenotypically and functionally different human NK cell subsets. *J.Immunol.* 2008;180:3739-3745.
280. Jacobsen N, Lonnqvist B, Ringden O et al. Graft-versus-leukaemia activity associated with cytomegalovirus seropositive bone marrow donors but separated from graft-versus-host disease in allograft recipients with AML. *Eur.J.Haematol.* 1987;38:350-355.
281. Nachbaur D, Clausen J, Kircher B. Donor cytomegalovirus seropositivity and the risk of leukemic relapse after reduced-intensity transplants. *Eur.J.Haematol.* 2006;76:414-419.
282. Fletcher JM, Prentice HG, Grundy JE. Natural killer cell lysis of cytomegalovirus (CMV)-infected cells correlates with virally induced changes in cell surface lymphocyte function-associated antigen-3 (LFA-3) expression and not with the CMV-induced down-regulation of cell surface class I HLA. *J.Immunol.* 1998;161:2365-2374.
283. Solana R, Tarazona R, Aiello AE et al. CMV and Immunosenescence: from basics to clinics. *Immun.Ageing* 2012;9:23.
284. van den Heuvel D, Jansen MAE, Nasserinejad K et al. Effects of nongenetic factors on immune cell dynamics in early childhood: The Generation R Study. *J.Allergy Clin.Immunol.* 2017;139:1923-1934.
285. van den Heuvel D, Jansen MA, Dik WA et al. Cytomegalovirus- and Epstein-Barr Virus-Induced T-Cell Expansions in Young Children Do Not Impair Naive T-cell Populations or Vaccination Responses: The Generation R Study. *J.Infect.Dis.* 2016;213:233-242.
286. Gamadia LE, van Leeuwen EM, Remmerswaal EB et al. The size and phenotype of virus-specific T cell populations is determined by repetitive antigenic stimulation and environmental cytokines. *J.Immunol.* 2004;172:6107-6114.
287. Bolland CM, Heslop HE. T cells for viral infections after allogeneic hematopoietic stem cell transplant. *Blood* 2016;127:3331-3340.
288. Feucht J, Opherk K, Lang P et al. Adoptive T-cell therapy with hexon-specific Th1 cells as a treatment of refractory adenovirus infection after HSCT. *Blood* 2015;125:1986-1994.
289. Creidy R, Moshous D, Touzot F et al. Specific T cells for the treatment of cytomegalovirus and/or adenovirus in the context of hematopoietic stem cell transplantation. *J.Allergy Clin.Immunol.* 2016;138:920-924.
290. Qasim W, Gilmour K, Zhan H et al. Interferon-gamma capture T cell therapy for persistent Adenoviraemia following allogeneic haematopoietic stem cell transplantation. *Br.J.Haematol.* 2013;161:449-452.
291. Peggs KS, Tholouli E, Chakraverty E et al. CMV~IMPACT: Results of a Randomized Controlled Trial of Immuno-Prophylactic Adoptive Cellular Therapy following Sibling Donor Allogeneic HSCT. *Blood* 2014;1109.

292. Blyth E, Clancy L, Simms R et al. Donor-derived CMV-specific T cells reduce the requirement for CMV-directed pharmacotherapy after allogeneic stem cell transplantation. *Blood* 2013;121:3745-3758.
293. Hatton O, Strauss-Albee DM, Zhao NQ et al. NKG2A-Expressing Natural Killer Cells Dominate the Response to Autologous Lymphoblastoid Cells Infected with Epstein-Barr Virus. *Front Immunol*. 2016;7:607.
294. Djaoud Z, Guethlein LA, Horowitz A et al. Two alternate strategies for innate immunity to Epstein-Barr virus: One using NK cells and the other NK cells and gammadelta T cells. *J.Exp.Med.* 2017
295. Chijioka O, Muller A, Feederle R et al. Human natural killer cells prevent infectious mononucleosis features by targeting lytic Epstein-Barr virus infection. *Cell Rep.* 2013;5:1489-1498.
296. Strowig T, Chijioka O, Carrega P et al. Human NK cells of mice with reconstituted human immune system components require preactivation to acquire functional competence. *Blood* 2010;116:4158-4167.
297. Carville A, Mansfield KG. Comparative pathobiology of macaque lymphocryptoviruses. *Comp Med.* 2008;58:57-67.
298. Wu C, Li B, Lu R et al. Clonal tracking of rhesus macaque hematopoiesis highlights a distinct lineage origin for natural killer cells. *Cell Stem Cell* 2014;14:486-499.
299. Ullah MA, Hill GR, Tey SK. Functional Reconstitution of Natural Killer Cells in Allogeneic Hematopoietic Stem Cell Transplantation. *Front Immunol*. 2016;7:144.
300. Mackay LK, Braun A, Macleod BL et al. Cutting edge: CD69 interference with sphingosine-1-phosphate receptor function regulates peripheral T cell retention. *J.Immunol.* 2015;194:2059-2063.
301. Shiow LR, Rosen DB, Brdickova N et al. CD69 acts downstream of interferon-alpha/beta to inhibit S1P1 and lymphocyte egress from lymphoid organs. *Nature* 2006;440:540-544.
302. Vales-Gomez M, Esteso G, Aydogmus C et al. Natural killer cell hyporesponsiveness and impaired development in a CD247-deficient patient. *J.Allergy Clin.Immunol.* 2016;137:942-945.
303. Shibata F, Toma T, Wada T et al. Skin infiltration of CD56(bright) CD16(-) natural killer cells in a case of X-SCID with Omenn syndrome-like manifestations. *Eur.J.Haematol.* 2007;79:81-85.
304. Bendall SC, Simonds EF, Qiu P et al. Single-cell mass cytometry of differential immune and drug responses across a human hematopoietic continuum. *Science* 2011;332:687-696.
305. Buettner F, Natarajan KN, Casale FP et al. Computational analysis of cell-to-cell heterogeneity in single-cell RNA-sequencing data reveals hidden subpopulations of cells. *Nat.Biotechnol.* 2015;33:155-160.
306. Inngjerdingen M, Damaj B, Maghazachi AA. Expression and regulation of chemokine receptors in human natural killer cells. *Blood* 2001;97:367-375.
307. Campbell JJ, Qin S, Unutmaz D et al. Unique subpopulations of CD56+ NK and NK-T peripheral blood lymphocytes identified by chemokine receptor expression repertoire. *J.Immunol.* 2001;166:6477-6482.
308. Berahovich RD, Lai NL, Wei Z, Lanier LL, Schall TJ. Evidence for NK cell subsets based on chemokine receptor expression. *J.Immunol.* 2006;177:7833-7840.
309. Heydtmann M, Lalor PF, Eksteen JA et al. CXC chemokine ligand 16 promotes integrin-mediated adhesion of liver-infiltrating lymphocytes to cholangiocytes and hepatocytes within the inflamed human liver. *J.Immunol.* 2005;174:1055-1062.
310. Germanov E, Veinotte L, Cullen R et al. Critical role for the chemokine receptor CXCR6 in homeostasis and activation of CD11d-restricted NKT cells. *J.Immunol.* 2008;181:81-91.
311. Hombrink P, Helbig C, Backer RA et al. Programs for the persistence, vigilance and control of human CD8+ lung-resident memory T cells. *Nat.Immunol.* 2016;17:1467-1478.
312. Morgan AJ, Guillen C, Symon FA et al. CXCR6 identifies a putative population of retained human lung T cells characterised by co-expression of activation markers. *Immunobiology* 2008;213:599-608.
313. Koopman LA, Kopcow HD, Rybalov B et al. Human decidual natural killer cells are a unique NK cell subset with immunomodulatory potential. *J.Exp.Med.* 2003;198:1201-1212.
314. Manaster I, Mizrahi S, Goldman-Wohl D et al. Endometrial NK cells are special immature cells that await pregnancy. *J.Immunol.* 2008;181:1869-1876.
315. Montaldo E, Vacca P, Chiassone L et al. Unique Eomes(+) NK Cell Subsets Are Present in Uterus and Decidua During Early Pregnancy. *Front Immunol*. 2015;6:646.
316. Fuchs A, Vermi W, Lee JS et al. Intraepithelial type 1 innate lymphoid cells are a unique subset of IL-12- and IL-15-responsive IFN-gamma-producing cells. *Immunity*. 2013;38:769-781.
317. Hanna J, Goldman-Wohl D, Hamani Y et al. Decidual NK cells regulate key developmental processes at the human fetal-maternal interface. *Nat.Med.* 2006;12:1065-1074.

318. Vacca P, Pietra G, Falco M et al. Analysis of natural killer cells isolated from human decidua: Evidence that 2B4 (CD244) functions as an inhibitory receptor and blocks NK-cell function. *Blood* 2006;108:4078-4085.
319. Woon HG, Braun A, Li J et al. Compartmentalization of Total and Virus-Specific Tissue-Resident Memory CD8+ T Cells in Human Lymphoid Organs. *PLoS Pathog.* 2016;12:e1005799.
320. Pallett LJ, Davies J, Colbeck EJ et al. IL-2high tissue-resident T cells in the human liver: Sentinels for hepatotropic infection. *J.Exp.Med.* 2017;214:1567-1580.
321. Purwar R, Campbell J, Murphy G et al. Resident memory T cells (T(RM)) are abundant in human lung: diversity, function, and antigen specificity. *PLoS One.* 2011;6:e16245.
322. Posavac CM, Zhao L, Dong L et al. Enrichment of herpes simplex virus type 2 (HSV-2) reactive mucosal T cells in the human female genital tract. *Mucosal Immunol.* 2017
323. Wilbanks A, Zondlo SC, Murphy K et al. Expression cloning of the STRL33/BONZO/TYMSTRligand reveals elements of CC, CXC, and CX3C chemokines. *J.Immunol.* 2001;166:5145-5154.
324. Matloubian M, David A, Engel S, Ryan JE, Cyster JG. A transmembrane CXC chemokine is a ligand for HIV-coreceptor Bonzo. *Nat.Immunol.* 2000;1:298-304.
325. Gough PJ, Garton KJ, Wille PT et al. A disintegrin and metalloproteinase 10-mediated cleavage and shedding regulates the cell surface expression of CXC chemokine ligand 16. *J.Immunol.* 2004;172:3678-3685.
326. van d, V, Verweij V, de Witte TM et al. An alternatively spliced CXCL16 isoform expressed by dendritic cells is a secreted chemoattractant for CXCR6+ cells. *J.Leukoc.Biol.* 2010;87:1029-1039.
327. Shimaoka T, Nakayama T, Kume N et al. Cutting edge: SR-PSOX/CXC chemokine ligand 16 mediates bacterial phagocytosis by APCs through its chemokine domain. *J.Immunol.* 2003;171:1647-1651.
328. Shimaoka T, Nakayama T, Fukumoto N et al. Cell surface-anchored SR-PSOX/CXC chemokine ligand 16 mediates firm adhesion of CXC chemokine receptor 6-expressing cells. *J.Leukoc.Biol.* 2004;75:267-274.
329. Mackay LK, Minnich M, Kragten NA et al. Hobit and Blimp1 instruct a universal transcriptional program of tissue residency in lymphocytes. *Science* 2016;352:459-463.
330. Tabata S, Kadokawa N, Kitawaki T et al. Distribution and kinetics of SR-PSOX/CXCL16 and CXCR6 expression on human dendritic cell subsets and CD4+ T cells. *J.Leukoc.Biol.* 2005;77:777-786.
331. Fahy OL, Townley SL, McColl SR. CXCL16 regulates cell-mediated immunity to *Salmonella enterica* serovar Enteritidis via promotion of gamma interferon production. *Infect.Immun.* 2006;74:6885-6894.
332. Veinotte L, Gebremeskel S, Johnston B. CXCL16-positive dendritic cells enhance invariant natural killer T cell-dependent IFNgamma production and tumor control. *Oncimmunology.* 2016;5:e1160979.
333. Yu J, Mao HC, Wei M et al. CD94 surface density identifies a functional intermediary between the CD56bright and CD56dim human NK-cell subsets. *Blood* 2010;115:274-281.
334. Romagnani C, Juelke K, Falco M et al. CD56bright CD16 - Killer Ig-Like Receptor - NK Cells Display Longer Telomeres and Acquire Features of CD56 dim NK Cells upon Activation. *J.Immunol.* 2007;178:4947-4955.
335. Sojka DK, Plougastel-Douglas B, Yang L et al. Tissue-resident natural killer (NK) cells are cell lineages distinct from thymic and conventional splenic NK cells. *Elife.* 2014;3:e01659.
336. Gineau L, Cognet C, Kara N et al. Partial MCM4 deficiency in patients with growth retardation, adrenal insufficiency, and natural killer cell deficiency. *J.Clin.Invest.* 2012;122:821-832.
337. Mace EM, Hsu AP, Monaco-Shawver L et al. Mutations in GATA2 cause human NK cell deficiency with specific loss of the CD56(bright) subset. *Blood* 2013;121:2669-2677.