

Principal Investigator/Program Director

Van den Brink, Marcel RM

NAME: van den Brink, Marcel R.M.		POSITION TITLE: Chief, Adult Allogeneic Bone Marrow Transplantation Service	
eRA COMMONS USER NAME: VANDENBRINK			
INSTITUTION AND LOCATION	DEGREE	YEAR(s)	FIELD OF STUDY
University of Leiden, Leiden, The Netherlands	B.S.	1982	Medicine
University of Leiden, Leiden, The Netherlands	M.S.	1985	Medicine
University of Leiden, Leiden, The Netherlands	M.D.	1986	Medicine
University of Leiden, Leiden, The Netherlands	Ph.D.	1991	Medicine (Immunology)

**A. Positions and Honors**

Internships, Residencies and Clinical Fellowships: 1990-1991: Resident in Internal Medicine, University Hospital, Leiden, The Netherlands; 1991-1993: Internship and Residency in Internal Medicine, Duke University Medical Center, Durham, NC; 1994-1997: Clinical Fellow in Hematology and Oncology, Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA

Clinical and Research Fellowships: 1986-1990: Research Fellow in Pathology and Immunohematology, University Hospital, Leiden, The Netherlands; 1987-1990: Postdoctoral Research Fellow, Pittsburgh Cancer Institute, Pittsburgh, PA; 1996-1999: Postdoctoral Research Fellow, Dana Farber Cancer Institute, Boston, MA

Positions and Appointments: 1997-1999: Attending Physician and Instructor in Hematology/Oncology, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA; 1999-2003: Assistant Member and Attending Physician, Allogeneic Bone Marrow Transplantation (ABMT) Service and Immunology Program, Memorial Sloan-Kettering Cancer Center (MSKCC), Memorial Hospital and Sloan-Kettering Institute (SKI), New York, NY; 2000-2003: Assistant Professor in Immunology, Weill Graduate School of Medical Sciences of Cornell University (WGSMS-CU), New York, NY; 2003-present: Associate Member, MSKCC, Immunology Program, SKI; Associate Attending Physician, ABMT Service, MSKCC; 2004-present: Chief, Adult ABMT Service, MSKCC.

Honors and Awards (selected): 1996 - Physician Scientist Award of the Howard Hughes Medical Institute; 1999 - Recipient of The Amy Strelzer Manasevit Scholar Award of the National Marrow Donor Program; 2000 - V Foundation Scholarship; 2000 - Damon Runyan Scholar Award of the Cancer Research Fund; 2004 - American Society of Clinical Investigation membership

**B. Selected peer-reviewed publications (selected from 43):**

3. **Van den Brink MRM**, Hunt LE, Hiserodt JC. In vivo treatment with monoclonal antibody 3.2.3 selectively eliminates natural killer cells in rats. *Journal of Experimental Medicine* 1990; 171:197-210.
4. **Van den Brink MRM**, Boggs SS, Herberman RB, Hiserodt JC. The generation of natural killer (NK) cells from NK precursor cells in rat long-term bone marrow cultures. *J. Exp. Med.* 1990; 172:303-313.
6. Ildstad ST, Wren SM, Boggs SS, Hronakes ML, Vecchini F, **van den Brink MRM**. Cross-species bone marrow transplantation: Evidence for tolerance induction, stem cell engraftment, and maturation of T lymphocytes in a xenogeneic stromal environment (rat to mouse). *J. Exp. Med.* 1991; 174:467-478.
14. **Van den Brink MRM**, Kapeller R, Pratt JC, Chang JH, Burakoff SJ. 1999. The extracellular receptor kinase (ERK) pathway is required for activation-induced cell death of T cells. *J. Biol. Chem.* 1999; 274: 11178-11185.
16. Pratt JC\*, **van den Brink MRM\***, Igras VE, Walk SF, Ravichandran KS, Burakoff SJ. Requirement for Shc in T cell antigen receptor-mediated activation of a T cell hybridoma. *Journal of Immunology* 1999;163:2586-2591. **\*shared first authorship**
17. **Van den Brink MRM**, Moore E, Horndasch KJ, Crawford JM, Hoffman J, Murphy GF, Burakoff SJ. Fas-deficient *lpr* mice are more susceptible to graft-versus-host disease. *Journal of Immunology* 2000; 164:469-480.
18. **Van den Brink MRM**, Moore E, Ferrara JLM, Burakoff SJ. Graft-versus-host disease-associated thymic damage results in the appearance of T cell clones with anti-host reactivity. *Transplantation* 2000; 69:446-449.
19. **Van den Brink MRM**, Moore E, Horndasch KJ, Crawford JM, Murphy GF, Burakoff SJ. Fas ligand-deficient *gld* mice are more susceptible to graft-versus-host disease. *Transplantation* 2000; 70:184-190.
21. Schmaltz C, Alpdogan O, Horndasch KJ, Muriglian SJ, Kappel BJ, Teshima T, Ferrara JLM, Burakoff SJ, **van den Brink MRM**. Differential use of Fas ligand and perforin cytotoxic pathways by donor T cells in graft-versus-host-disease and graft-versus-leukemia. *Blood* 2001; 97:2886-2895.

22. Alpdogan O, Schmaltz C, Muriglan SJ, Kappel BJ, Perales MA, Rotolo JA, Halm JA, Rich BE, **van den Brink MRM**. Administration of Interleukin-7 after allogeneic bone marrow transplantation improves immune reconstitution without aggravating graft-versus-host-disease. *Blood* 2001; 98:2256-2265.
25. Schmaltz C, Alpdogan O, Kappel BJ, Muriglan SJ, Rotolo JA, Ongchin J, Willis LM, Greenberg AS, Eng JM, Crawford JM, Murphy GF, Yagita H, Walczak H, Peschon J, **van den Brink MRM**. T cells require TRAIL for optimal graft-versus-tumor activity. *Nature Medicine* 2002; 8:1433-37.
26. Schmaltz C, Alpdogan O, Muriglan SJ, Kappel BJ, Rotolo JA, Ricchetti ET, Greenberg AS, Willis LM, Murphy GF, Crawford JM, **van den Brink MRM**. Donor T cell-derived TNF is required for graft-versus-host disease and graft-versus-tumor activity after bone marrow transplantation. *Blood* 2003; 101:2440-2445.
27. Alpdogan O, Schmaltz C, Muriglan SJ, Doubrovina E, Schiro R, Kappel BJ, Greenberg AS, Willis LM, Rotolo JA, O'Reilly RJ, **van den Brink MRM**. Insulin Growth Factor-I (IGF-I) enhances lymphoid and myeloid reconstitution after allogeneic bone marrow transplantation. *Transplantation* 2003; 75: 1977-1983.
28. Alpdogan O, Muriglan SJ, Eng J, Willis LM, Greenberg AS, **van den Brink MRM**. Interleukin-7 enhances peripheral T cell reconstitution after allogeneic hematopoietic stem cell transplantation. *J. Clin. Invest.* 2003; 112: 1095-1107.
29. Petrovic A, Alpdogan O, Willis LM, Eng JF, Greenberg AS, Kappel BJ, Liu C, Murphy G, Heller G, **van den Brink MRM**. LPAM ( $\alpha_4\beta_7$   $\square$  integrin) is an important homing integrin on alloreactive T cells in the development of intestinal Graft-Versus-Host Disease. *Blood* 2004; 103: 1542-1547.
31. Sugeran PB, Faber S, Willis LM, Murphy GF, Pappo J, Silberstein D, **van den Brink MRM**. Kinetics of gene expression in murine cutaneous graft-versus-host disease. *Am. J. Pathol.* 2004; 164: 2189-2202.
33. Muriglan SJ, Ramirez-Montagut T, Alpdogan O, van Huystee TW, Eng JM, Hubbard VM, Kochman AA, Tjoe KH, Riccardi C, Pandolfi PP, Sakaguchi S, Houghton AN, **van den Brink MRM**. GITR Activation Induces an Opposite Effect on Alloreactive CD4+ and CD8+ T Cells in Graft-versus-Host Disease. *J. Exp. Med.* 2004; 200:149-157.
34. Alpdogan O, Muriglan SJ, Eng JM, Willis LM, Tjoe KH, Hubbard VM, **van den Brink MRM**. Interleukin-15 enhances immune reconstitution after allogeneic bone marrow transplantation. *Blood* 2005; 105: 865-873.
35. Hubbard VM, Eng JM, Ramirez-Montagut T, Tjoe KH, Muriglan SJ, Kochman AA, Terwey TH, Willis LM, Schiro R, Heller G, Murphy GF, Liu C, Alpdogan O, **van den Brink MRM**. Absence of inducible costimulator on alloreactive T cells reduces graft-versus-host disease and induces Th2 deviation. *Blood* 2005; 106:3285-3292.
36. Terwey TH, Kim TD, Kochman AA, Hubbard VM, Lu SX, Zakrzewski JL, Ramirez-Montagut T, Eng JM, Muriglan SJ, Heller G, Murphy GF, Liu C, Budak-Alpdogan T, Alpdogan O, **van den Brink MRM**. CC chemokine receptor 2 is required for CD8-induced graft-versus-host disease. *Blood* 2005; 106:3322-3330.
37. Waldman E, Hubbard VM, Kochman AA, Eng JM, Terwey TH, Muriglan SJ, Lu SX, Kim TD, Heller G, Murphy GF, Liu C, Alpdogan O, **van den Brink MRM**. Absence of the  $\beta 7$  integrin results in less graft-versus-host disease due to decreased homing of alloreactive T cells to the intestine. *Blood* 2006; 107:1703-1711.
38. Kappel BJ, Pinilla-Ibarz J, Eng JM, **van den Brink MRM\***, Scheinberg DA\*. Depletion of Specific Immunity: Retention of Graft-Versus-Tumor Activity Without Graft-Versus-Host-Disease. *Blood* 2006; 107:2045-2051. **\*these authors contributed equally**
39. Alpdogan O, Hubbard VM, Smith OM, Patel N, Goldberg GL, Gray DH, Lu S, Kochman AA, Eng JM, Muriglan SJ, Boyd RL, **van den Brink MRM**. Keratinocyte growth factor (KGF) is required for post-natal thymic regeneration. *Blood* 2006; 107:2453-2460
41. Ramirez-Montagut T, Chow A, Hirschhorn-Cymerman D, Terwey TH, Hubbard VM, Kochman AA, Lu SX, Miles RC, Sakaguchi S, Houghton AN, **van den Brink MRM**. GITR Activation Breaks Self-Tolerance to Melanoma Differentiation Antigens and Enhances Anti-Tumor Immunity. *Journal of Immunology* 2006 (in press).
42. Perales M-A, Diab A, Cohen AD, Huggins DW, Guevara-Patino JA, Hubbard VM, Engelhorn ME, Kochman AA, Eng JM, Alpdogan O, Terwey TH, Wolchok JD, Houghton AN, **van den Brink MRM**. DNA immunization against melanoma antigens enhances tumor immunity after allogeneic hematopoietic stem cell transplantation. *Journal of Immunology* (in press).
43. Zakrzewski JL, Kochman AA, Lu SX, Terwey TH, Kim TD, Hubbard VM, Muriglan SJ, Suh D, Cabrera-Perez J, Radhakrishnan R, Heller G, Zuniga-Pflucker JC, Alpdogan O, **van den Brink MRM**. Adoptive transfer of *in vitro* generated T cell precursors enhances donor T cell reconstitution in allogeneic hematopoietic stem cell transplantation recipients. *Nature Medicine* (in press).



Marcel R.M. van den Brink (PI) 07/01/2001-06/30/2004  
Cancer Research Fund of the Damon Runyan-Walter Winchell Foundation  
*The role of TRAIL in bone marrow transplantation.*  
This is a research career development award.

Marcel R.M. van den Brink 07/01/2001-06/30/2002  
Wendy Will Case Cancer Fund  
*The role of TRAIL in bone marrow transplantation.*  
The major goal of this project is to analyze the role of TRAIL in murine bone marrow transplantation models.

SBIR-AT-NIAID PA-01-052 Michael Rosenzweig (PI) 06/01/2003-12/01/2004  
NIH/NIAID  
*Immune Reconstitution using a thymic organoid in a murine model of bone marrow transplantation*  
The major goals of this project are to evaluate the use of a novel thymic organoid to generate ex vivo donor T lymphocytes and their contribution to post-transplant immune reconstitution in murine bone marrow transplantation models.

Juri Gelovani (PI) 09/01/2002-08/31/2005  
Department of Energy/Office of Science  
*PET imaging of adoptive progenitor cell therapies*  
The major goals of this project are to evaluate different PET-reporter imaging approaches to monitor the fate of hematopoietic and other progenitor cells in a variety of mouse models.

RO1 HL69929-01 Marcel R.M. van den Brink (PI) 12/12/2001-11/30/2005  
NIH/NHLBI  
*Strategies to enhance immune reconstitution after BMT*  
The major goals of this project are to analyze in murine bone marrow transplantation models the use of immunostimulatory cytokines to enhance immune reconstitution after allogeneic bone marrow transplantation without aggravating GVHD activity and while sparing GVT activity.

Translational Research Award Marcel R.M. van den Brink (PI) 10/01/2005 – 09/30/2007  
The Leukemia & Lymphoma Society  
*Interleukin-7 as a novel therapy to overcome post-transplant immunoincompetence in recipients of allogeneic stem cell grafts.*  
The major goals of this project are to perform immune reconstitution analyses on patients treated with human recombinant Interleukin-7.