

Associate Professor Mirjam H. M. Heemskerk
Head of the Laboratory of Experimental Hematology, Department of Hematology
Leiden University Medical Center, Leiden, The Netherlands

CAREER SUMMARY

- 2008–present Associate Professor, staff-member, and Head of the Laboratory of Experimental Hematology at the Department of Hematology, LUMC.
- 2001 - 2008 Assistant Professor at the Department of Hematology, LUMC.
- 1999 - 2001 Gisela Thier Fellowship at the Department of Hematology, LUMC.
- 1998 - 1999 Postdoctoral Fellowship at the Department of Hematology, Leiden University Medical Center, The Netherlands.
- 1994 - 1998 Postdoctoral Fellowship at the Division of Immunology, Netherlands Cancer Institute, Amsterdam, The Netherlands.
- 1990 – 1994 PhD student at the Division of Immunology of the Veterinary Faculty Utrecht, The Netherlands.

EDUCATION

Date (mm/yy)	Qualification	Subject	Organisation
03/1995	PhD	Immunology	Utrecht University
08/1990	MSc	Biomedical Sciences, track Immunology	Leiden University

SUPERVISORY RESPONSIBILITY FOR PhD STUDENTS (COPROMOTOR)

- 2001-2006 L.T.J.N. van der Veken: Title thesis: *Design of novel TCR gene therapy strategies for the treatment of haematological malignancies* (09/2009)
- 2003-2009 M.M. van Loenen: Title thesis: *Designing T cells with desired T cell receptor make-up for immunotherapy* (05/2011)
- 2005-2009 A.L. Amir: Title Thesis: *The benefits and threats of allo-HLA reactive T cells* (06/2012)
- 2007-2013 P. Hombrink: Title thesis: *SNP-based genome-wide identification of hematopoiesis-restricted minor histocompatibility antigens* (09/ 2014).
- 2009-2015 H. Jolink: Title thesis: *Human T-cell responses to Aspergillus fumigatus – in healthy individuals and patients with Aspergillus-related disease* (03/2017).
- 2011-2015 L. Jahn: Title thesis: *Exploiting HLA-alloreactivity for TCR gene therapy of B cell malignancies* (04/2017).
- 2014-2017 I. Bijlen: Title project: *Large scale discovery of minor histocompatibility antigens valuable for immunotherapy of hematological tumors.*

- 2015-2019 M. Meeuwsen: Title project: *High affinity T cell receptor library for targeting B-cell malignancies.*
- 2016-2020 M. de Rooij: Title project: *Identification of new cancer associated peptides and the respective identification of high affinity TCRs directed against these.*
- 2016-2020 Rosa van Amerongen: Title project: *Search for a library of ovarian tissue specific TCRs.*

INTERNATIONAL ACTIVITIES

REVIEWER INTERNATIONAL JOURNALS:

Blood, Haematologica, Science Translational Medicine, Cancer Research, Leukemia, Journal of Immunology, Clinical Cancer Research, Expert Opinion On Biological Therapy, European Journal of Immunology, Human Gene Therapy, Journal of Translational Medicine, Journal of Experimental & Clinical Cancer Research, Clinical Immunology, Cancer Immunology Immunotherapy, Gene therapy, Mucosal Immunology, Frontiers in T cell biology, Cell report.

REVIEWER AND ADVISOR PROJECTS:

Member of the Scientific Advisory Council of the Landsteiner Foundation (LSBR) (from 2012 till present), Member of the Review Committee of the Rubicon Life Sciences (ALW and Zon-MW), KWF Kankerbestrijding, Zon-MW, Leukemia Research, Children with Leukemia, Association for international cancer research (AICR), Der Wissenschaftsfonds (FWF), Leukemia and lymphoma Research, European Science Foundation, The Wellcome Trust, French NCI, Institute National de Cancer, KIKA.

ORGANISOR OF MEETINGS:

- 2007–2012 Organiser of the annual Dutch Tumor Immunology Meeting (KWF Deelwerkgemeenschap tumor-immunologie en Zon-MW)
- 2011-present Scientific committee Nederlandse Vereniging voor Immunologie.
- 2012-2016 Scientific committee Nederlandse Vereniging voor Gen en Cel Therapie.
- 2012-2016 Scientific committee Nederlandse Vereniging voor Hematologie.
- 2015 Scientific committee of the European Society for Gene and Cell Therapy Conference in The Haque

ACADEMIC ACTIVITIES

- 2014 -present Board of education committee M.Sc. Biomedical Sciences, LUMC
- 2010 -2014 Board of examiners M.Sc. Biomedical Sciences, LUMC
- 2010 -2012 Lecturer in M.Sc. Medical Biology course 'Tumor Immunology', VUMC,

Amsterdam

- 2009 -present Talent coach of excellent B.Sc. Biomedical Sciences students, LUMC
2002 -present Coordinator of the Frontiers of Science M.Sc. course 'Allogeneic transplantation and immunotherapy; from bench to bedside'
2002 -present Lecturer and workgroup leader in Frontiers of Science M.Sc. Course: 'Allogeneic transplantation and immunotherapy; from bench to bedside'
2002 -2014 Lecturer in LIFI course for research technicians

GRANTS, SCHOLARSHIPS AND PRIZES

- 2016: SRA met Bellicum Pharmaceuticals: Identification of high affinity TCRs directed against cancer associated antigens. **PI** **2.547.415€**
- 2016: ITN Marie Curie Horizon 2020 EN-ACTI²NG: European Network on Anti-Cancer Immuno-Therapy Improvement by modification of CAR and TCR Interactions and Nanoscale Geometry **PI**. **255.374€**
- 2015: KWF UL2015-7830: Construction of a safe and efficient chimeric TCR modified cell product for the treatment of cancer **PI**. **579.406€**
- 2015: SRA met Bellicum Pharmaceuticals : 'Generation of a high affinity T-cell receptor library for targeting POU2AF1/Bob1 and PRAME' **PI**. **350.000€**
- 2014: KWF UL 2014-6831: 'High affinity T cell receptor library for targeting B-cell malignancies' **PI**. **567.200€**
- 2013: LSBR 1331: 'Large scale discovery of leukemia specific minor histocompatibility antigens valuable for immunotherapy of hematological tumors' **PI**. **225.500€**
- 2012: KWF UL-2012-5552: 'High affinity PRAME specific T cell receptor (TCR) for gene therapy of patients with solid tumors' **PI**. **252.750€**
- 2011: Jan Swammerdam Prize: received from the Dutch Society of Hematology **40.000€**
- 2010: KWF UL 2010-4832: 'Selection of high affinity tumor specific T cell receptors for TCR gene therapy of cancer patients' **PI**. **550.000€**
- 2009: Schering-Plough 2009 unrestricted grant. 'T cell immunity against Aspergillus Fumigates' **PI**. **25.000€**
- 2007: Zon-MW 2007-4330000: 'Retroviral gene transfer of T cell receptor recognizing minor histocompatibility antigens to virus specific T cells as cellular immunotherapy of patients with hematological malignancies after allogeneic stem cell transplantation' **PI**. **1.200.000€**
- 2007: KWF UL 2007-3825: 'SNP-based genome-wide identification of hematopoiesis-restricted minor histocompatibility antigens' **PI**. **465.000€**
- 2007: KWF UL 2007-3927: 'Development of a standard operating procedure for generation of mHag TCR-transduced virus specific T cell lines for cellular immunotherapy' **co-applicant**. **90.000€**
- 2006: LSBR 2006-0611: Characterisation of the alloimmune response after HLA mismatched stem cell transplantation' **PI**. **350.000€**
- 2005: KWF UL 2005-3251: 'Engineering of TCR-transferred T cells with optimal TCR make-up for effective anti-leukemic reactivity and

	persistence in vivo' PI .	
2001:	<u>KWF UL 2001-2490</u> : 'Genetic modification of T lymphocytes to rescue and redirect antigen specificity for immunotherapy' PI .	325.000€
1999:	<u>Gisela Thier Fellowship</u> : 'Rescue of T lymphocyte proliferation and specificity by retroviral gene transfer'.	120.000€

PATENTS

US Serial No. 62/074,534, filed November 3, 2014, entitled "T CELL RECEPTORS DIRECTED AGAINST BOB1 AND USES THEREOF."

US Serial No. 62/130,884, filed March 10, 2015, entitled "T-CELL RECEPTORS DIRECTED AGAINST THE PREFERENTIALLY EXPRESSED ANTIGEN OF MELANOMA AND USES THEREOF."

LICENCE AGREEMENT

Licence agreement with Bellicum Pharmaceuticals, signed March 30, 2015, to test the TCRs directed against PRAME and Bob1 in clinical studies and to develop these TCRs towards commercial application.

OUTPUT INDICATORS

Number of publications: 98; 1st author: 13; Senior author: 30; H-factor: 30
Total number of cites: >3360; Average number of cites/article: 37.

REFERENCES

1. Jahn, L., P. Hombrink, R. S. Hagedoorn, M. G. Kester, D. M. van der Steen, T. Rodriguez, and T. Pentcheva-Hoang, A. H. de Ru, M. P. Schoonakker, M. H. Meeuwse, M. Griffioen, P. A. van Veelen, J. H. Falkenburg and **M. H. Heemskerk** 2017. TCR-based cellular therapy for multiple myeloma and other B-cell malignancies by targeting intracellular transcription factor BOB1. *Blood* 2016-09-737536. doi: 10.1182/blood-2016-09-737536. [Epub ahead of print]
2. van Bergen, C. A., S. A. van Luxemburg-Heijs, L. C. de Wreede, M. Eefting, P. A. von dem Borne, B. P. van, **M. H. Heemskerk**, A. Mulder, F. H. Claas, M. A. Navarrete, W. M. Honders, C. E. Rutten, H. Veelken, I. Jedema, C. J. Halkes, M. Griffioen, and J. H. Falkenburg. 2017. Selective graft-versus-leukemia depends on magnitude and diversity of the alloreactive T cell response. *J. Clin. Invest.* pii: 86175. doi: 10.1172/JCI86175. [Epub ahead of print]
3. Jolink, H., B. R. de, P. Hombrink, R. E. Jonkers, J. T. van Dissel, J. H. Falkenburg, and **M. H. Heemskerk**. 2016. Pulmonary immune responses against *Aspergillus fumigatus*

are characterized by high frequencies of IL-17 producing T-cells. *J.Infect.* 74(1):81-88.

4. Jahn,L., R.S.Hagedoorn, D.M.van der Steen, P.Hombrink, M.G.Kester, M.P.Schoonakker, R.D.de, P.A.van Veelen, J.H.Falkenburg, and **M.H.Heemskerk**. 2016. A CD22-reactive TCR from the T-cell allorepertoire for the treatment of acute lymphoblastic leukemia by TCR gene transfer. *Oncotarget* 7(44):71536-71547.
5. Jahn,L., D.M.van der Steen, R.S.Hagedoorn, P.Hombrink, M.G.Kester, M.P.Schoonakker, D.Ridder, P.A.van Veelen, J.H.Frederik Falkenburg, and **M.H.Heemskerk**. 2016. Generation of CD20-specific TCRs for TCR gene therapy of CD20low B-cell malignancies insusceptible to CD20-targeting antibodies. *Oncotarget* 7(47):77021-77037.
6. Gram,A.M., T.Oosenbrug, M.F.Lindenbergh, C.Bull, A.Comvalius, K.J.Dickson, J.Wiegant, H.Vrolijk, R.J.Lebbink, R.Wolterbeek, G.J.Adema, M.Griffioen, **M.H.Heemskerk**, D.C.Tscharke, L.M.Hutt-Fletcher, E.J.Wiertz, R.C.Hoeben, and M.E.Ressing. 2016. The Epstein-Barr Virus Glycoprotein gp150 Forms an Immune-Evasive Glycan Shield at the Surface of Infected Cells. *PLoS.Pathog.* 12:e1005550.
7. Breman,E., J.M.Ruben, K.L.Franken, **M.H.Heemskerk**, D.L.Roelen, F.H.Claas, and K.C.van. 2016. Uptake of HLA Alloantigens via CD89 and CD206 Does Not Enhance Antigen Presentation by Indirect Allorecognition. *J.Immunol.Res.* 2016:4215684.
8. Hutten,T.J., S.Thordardottir, H.Fredrix, L.Janssen, R.Woestenenk, J.Tel, B.Joosten, A.Cambi, **M.H.Heemskerk**, G.M.Franssen, O.C.Boerman, L.B.Bakker, J.H.Jansen, N.Schaap, H.Dolstra, and W.Hobo. 2016. CLEC12A-Mediated Antigen Uptake and Cross-Presentation by Human Dendritic Cell Subsets Efficiently Boost Tumor-Reactive T Cell Responses. *J.Immunol.* 197:2715-2725.
9. Frosig,T.M., J.Yap, T.Seremet, R.Lyngaa, I.M.Svane, S.P.Thor, **M.H.Heemskerk**, G.M.Grotenbreg, and S.R.Hadrup. 2015. Design and validation of conditional ligands for HLA-B*08:01, HLA-B*15:01, HLA-B*35:01, and HLA-B*44:05. *Cytometry A* 87:967-975.
10. de Mare-Bredemeijer,E.L., X.L.Shi, S.Mancham, G.R.van, M.Heide-Mulder, R.de Boer, **M.H.Heemskerk**, J.J.de, L.J.van der Laan, H.J.Metselaar, and J.Kwekkeboom. 2015. Cytomegalovirus-Induced Expression of CD244 after Liver Transplantation Is Associated with CD8+ T Cell Hyporesponsiveness to Alloantigen. *J.Immunol.* 195:1838-1848.
11. Jolink,H., R.de Boer, L.N.Willems, J.T.van Dissel, J.H.Falkenburg, and **M.H.Heemskerk**. 2015. T helper 2 response in allergic bronchopulmonary aspergillosis is not driven by specific Aspergillus antigens. *Allergy* 70:1336-1339.
12. Spel,L., J.J.Boelens, D.M.van der Steen, N.J.Blokland, M.M.van Noesel, J.J.Molenaar,

- M.H.Heemskerk**, M.Boes, and S.Nierkens. 2015. Natural killer cells facilitate PRAME-specific T-cell reactivity against neuroblastoma. *Oncotarget*. 6:35770-35781.
13. Hombrink,P., C.Hassan, M.G.Kester, L.Jahn, M.J.Pont, A.H.de Ru, C.A.van Bergen, M.Griffioen, J.H.Falkenburg, P.A.van Veelen, and **M.H.Heemskerk**. 2015. Identification of biological relevant minor histocompatibility antigens within the B-lymphocyte derived HLA-ligandome using a reverse immunology approach. *Clin.Cancer Res*. 21(9):2177-86
 14. Hassan,C., E.Chabrol, L.Jahn, M.G.Kester, A.H.de Ru, J.W.Drijfhout, J.Rossjohn, J.H.Falkenburg, **M.H.Heemskerk**, S.Gras, and P.A.van Veelen. 2015. Naturally processed non-canonical HLA-A*02:01 presented peptides. *J.Biol.Chem*. 290:2593-2603.
 15. Pellicci,D.G., A.P.Uldrich, N.J.Le, F.Ross, E.Chabrol, S.B.Eckle, B.R.de, R.T.Lim, K.McPherson, G.Besra, A.R.Howell, L.Moretta, J.McCluskey, **M.H.Heemskerk**, S.Gras, J.Rossjohn, and D.I.Godfrey. 2014. The molecular bases of delta/alphabeta T cell-mediated antigen recognition. *J.Exp.Med*. 211:2599-2615.
 16. Jahn,L., P.Hombrink, C.Hassan, M.G.Kester, D.M.van der Steen, R.S.Hagedoorn, J.H.Falkenburg, P.A.van Veelen, and **M.H.Heemskerk**. 2015. Therapeutic targeting of the BCR-associated protein CD79b in a TCR-based approach is hampered by aberrant expression of CD79b. *Blood* 125:949-958.
 17. Flinsenbergt,W., L.Spel, M.Jansen, D.Koning, H.C.de, M.Plantinga, R.Scholman, M.M.van Loenen, S.Nierkens, L.Boon, B.D.van, **M.H.Heemskerk**, J.J.Boelens, and M.Boes. 2015. Cognate CD4 T-cell licensing of dendritic cells heralds anti-cytomegalovirus CD8 T-cell immunity after human allogeneic umbilical cord blood transplantation. *J.Virol*. 89:1058-1069.
 18. van Loenen,M.M., R.de Boer, E.van Liempt, P.Meij, I.Jedema, J.H.Falkenburg, and **M.H.Heemskerk**. 2014. A Good Manufacturing Practice procedure to engineer donor virus-specific T cells into potent anti-leukemic effector cells. *Haematologica* 99:759-768.
 19. Jolink,H., R.S.Hagedoorn, E.L.Lagendijk, J.W.Drijfhout, J.T.van Dissel, J.H.Falkenburg, and **M.H.Heemskerk**. 2014. Induction of *A. fumigatus*-specific CD4-positive T cells in patients recovering from invasive aspergillosis. *Haematologica* 99:1255-1263.
 20. Snauwaert,S., G.Verstichel, S.Bonte, G.Goetgeluk, S.Vanhee, C.Y.Van, M.K.De, C.Heirman, H.Stauss, **M.H.Heemskerk**, T.Taghon, G.Leclercq, J.Plum, A.W.Langerak, K.Thielemans, T.Kerre, and B.Vandekerckhove. 2014. In vitro generation of mature, naive antigen-specific CD8(+) T cells with a single T-cell receptor by agonist selection. *Leukemia* 28:830-841.

21. Breman,E., P.P.van Miert, D.M.van der Steen, **M.H.Heemskerk**, I.I.Doxiadis, D.Roelen, F.H.Claas, and K.C.van. 2014. HLA monomers as a tool to monitor indirect allorecognition. *Transplantation* 97:1119-1127.
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23. G. Lugthart, M.M. van Ostaijen-Ten Dam, C.M. Jol-van der Zijde, T.C. van Holten, M.G. Kester, **M.H. Heemskerk**, R.G. Bredius, M.J. van Tol, A.C. Lankester. 2014 Early Cytomegalovirus Reactivation Leaves a Specific and Dynamic Imprint on the Reconstituting T Cell Compartment Long-Term after Hematopoietic Stem Cell Transplantation. *Biol Blood Marrow Transplant* 20:655-661,.
24. Linnemann,C., B.Heemskerk, P.Kvistborg, R.J.Kluin, D.A.Bolotin, X.Chen, K.Bresser, M.Nieuwland, R.Schotte, S.Michels, R.Gomez-Eerland, L.Jahn, P.Hombrink, N.Legrand, C.J.Shu, I.Z.Mamedov, A.Velds, C.U.Blank, J.B.Haanen, M.A.Turchaninova, R.M.Kerkhoven, H.Spits, S.R.Hadrup, **M.H.Heemskerk**, T.Blankenstein, D.M.Chudakov, G.M.Bendle, and T.N.Schumacher. 2013. High-throughput identification of antigen-specific TCRs by TCR gene capture. *Nat.Med.* 19:1534-1541.
25. Hombrink,P., Y.Raz, M.G.Kester, R.de Boer, B.Weissbrich, P.A.von dem Borne, D.H.Busch, T.N.Schumacher, J.H.Falkenburg, and **M.H.Heemskerk**. 2013. Mixed functional characteristics correlating with TCR-ligand koff -rate of MHC-tetramer reactive T cells within the naive T-cell repertoire. *Eur.J.Immunol.* 43:3038-3050.
26. van Loenen,M.M., R.S.Hagedoorn, R.de Boer, J.H.Falkenburg, and **M.H.Heemskerk**. 2013. Extracellular domains of CD8alpha and CD8beta subunits are sufficient for HLA class I restricted helper functions of TCR-engineered CD4+ T cells. *PLoS.One.* 8:e65212.
27. Jolink,H., I.C.Meijssen, R.S.Hagedoorn, M.Arentshorst, J.W.Drijfhout, A.Mulder, F.H.Claas, J.T.van Dissel, J.H.Falkenburg, and **M.H.Heemskerk**. 2013. Characterization of the T-cell-mediated immune response against the *Aspergillus fumigatus* proteins Crf1 and catalase 1 in healthy individuals. *J.Infect.Dis.* 208:847-856.
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35. Amir, A.L., D.M. van der Steen, M.M. van Loenen, R.S. Hagedoorn, R. de Boer, M.G. Kester, A.H. de Ru, G.J. Lugthart, C. van Kooten, P.S. Hiemstra, I. Jedema, M. Griffioen, P.A. van Veelen, J.H. Falkenburg, and **M.H. Heemskerk**. 2011. PRAME specific allo-HLA restricted T-cells with potent antitumor reactivity useful for therapeutic T cell receptor gene transfer. *Clin. Cancer Res.* aug epub.
36. Falkenburg, W.J., J.J. Melenhorst, M. van de Meent, M.G. Kester, P. Hombrink, **M.H. Heemskerk**, R.S. Hagedoorn, E. Gostick, D.A. Price, K. Rezvani, J.H. Falkenburg, A. J. Barrett, and I. Jedema. 2011. Allogeneic HLA-A*02-restricted WT1-specific T cells from mismatched donors are highly reactive but show off-target promiscuity. *J. Immunology* 187:2824.
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42. **Heemskerk, M.H.** 2010. T-cell receptor gene transfer for the treatment of leukemia and other tumors. *Haematologica* 95:15.
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therapy. *Haematologica* 2009;94:1316.

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