CURRICULUM VITAE (maximum 4 pages)

Part A. PERSONAL INFORMATION

CV date	10/01/2017

First and Family name	*Hisse Martien van Santen*		
Researcher numbers	Researcher ID	*E-8103-2013*	
	Orcid code		

A.1. Current position

Name of University/Institution	*Consejo Superior de Investigaciones Científicas, Centro Biología Molecular Severo Ochoa*		
Department	*Cell Biology and Immunology*		
Address and Country	*Calle Nicolás Cabrera 1, 28049 Madrid, Spain*		
Phone number	*+34911964682*	E-mail	*hvansanten (at) cbm.csic.es*
Current position	*Científico Titular*	From	2008
Expertise (UNESCO)	*2412 Immunology*		
Keywords	*T cell Receptor - differentiation - T cell activation - murine models*		

A.2. Education

Academic degrees	University	Year
Drs (MSc) medical biology	*Vrije Universiteit Amsterdam, NL*	*1991*
PhD cell biology/immunology	*Vrije Universiteit Amsterdam, NL*	*1996*

A.3. JCR articles, h Index, thesis supervised…

- 21 articles (16/21 in Q1; 6/21 1st author; 4/21 corresponding author) published since 1991 in, amongst others, Immunity, J. Exp. Med, PNAS, J. Cell Biol, J. Immunol. PLoS Comp. Biol.; h-index: 13; total citations: 1125; avg. citations/article: 59; avg. citations/year last 5 years: 72; (source: WoS)
- Number of 'sexenios' conferred: 3 (latest 31/12/2014)
- supervision of 2 completed and 1 ongoing doctoral thesis
- supervision of 3 undergraduate thesis and 1 master thesis

Part B. CV SUMMARY

My research has focused on understanding the interaction between the T cell Receptor (TCR) and Major Histocompatibility Complex (MHC) molecules loaded with peptides (pMHC) and how the quality of this interaction and the molecular organization of these receptors and ligands affects T cell function.

During my PhD thesis work, performed under guidance of Drs. Hidde Ploegh and Anton Berns at the Netherlands Cancer Institute (Amsterdam, NL) and MIT (Cambridge, MA), I developed mouse models impaired in loading of MHC class I molecules with antigenic and endogenous peptides and used these models to address the role of MHC-bound peptides in assembly, transport and stability of the MHC complexes in vivo and showed that generation of a diverse T cell repertoire during thymic differentiation can occur quite efficiently in the context of a limited pMHC repertoire.

I honed my skills in working with murine models relevant for understanding TCR – MHCp interactions and T cell function in the laboratory of Drs. Diane Mathis and Christophe Benoist (IGBMC, Illkirch, FR and Harvard Medical School, Boston, MA). I generated mouse strains that allowed spatio-temporal and quantitative control of MHC-mediated antigenic peptide presentation using a tetracycline regulated gene expression system. I could show that the amount of antigenic pMHC encountered by T cells in the thymus had little effect on the efficiency of their differentiation into regulatory T cells, suggesting that their differentiation is limited by particular niches in the thymus. Together with Reinhard Obst, I found that extended times of antigen presentation by non-activated DCs in vivo could compensate for DC activation-dependent co-stimulation, indicating that one function of co-stimulation is allowing shorter exposure times of T cells to antigenic DCs and thus allowing more

efficient T cell activation. My stay at this laboratory was supported by postdoctoral fellowships from EMBO, the Cancer Research Institute and the Leukemia & Lymphoma Society.

Since 2004 I have worked at the CBMSO (Madrid, ES), first as a Ramon y Cajal fellow with Dr. Balbino Alarcon and since 2008 as Científico Titular of the CSIC. The main focus of my research is understanding how pre-grouping of non-activated TCRs into nanoclusters affects the functional capacity of T cells. In collaboration with Dr. Alarcon, we showed that the extent of TCR nanoclustering is regulated during differentiation of naïve T cells in vitro and in vivo and that the increase in TCR nanoclustering observed in memory T cells underlies their increased sensitivity to antigen. We generated mouse lines transgenic for a mutant TCR-associated ζ chain that impairs TCR nanoclustering. Our latest findings indicate defects in early steps of T cell differentiation in the thymus and phenotypic changes in mature T cells that are compatible with altered TCR signaling capacities. We will test how these defects impair auto-immune and anti-tumor responses in order to determine whether TCR nanoclusters could be relevant therapeutic targets.

I am the coordinator of a group of European laboratories and companies that aim to define and improve tumor-recognizing TCRs and CARs, bringing together experts in development and preclinical testing of new receptors with groups that can describe their molecular organization and interaction dynamics down to the single molecule level. The ability to correlate the degree of functionality with the molecular details of their interactions and organization and should provide rational means to improve their function. We have obtained funding from the H2020 MSCA Innovative Training Network (EN-ACTI^{2}NG, project nº 721358).

This network provides an important synergy to our recently started line of more applied research to develop new types of tumor-recognizing recombinant receptors based on our understanding of the basic aspects of TCR mediated signaling. The goal is to develop more tumor-specific receptors in order to reduce the sometimes severe off-tumor/on-target side effects of currently used receptors.

Part C. RELEVANT MERITS

C.1. Publications, including books *(most relevant of last 10 years)*

Original articles:

Castro M*, **van Santen HM***, Ferez M, Alarcón B, Lythe GD, Molina-Paris C (2014). Receptor Pre-Clustering and T cell Responses: Insights into Molecular Mechanisms. **Front. Immunol**. 5, 132; doi: 10.3389/fimmu.2014.00132 (*: co-corresponding authors).

Férez M, Castro M, Alarcon B*, **van Santen HM*** (2014). Cognate peptide-MHC complexes are expressed as tightly apposed nanoclusters in virus-infected cells to allow TCR crosslinking. **J. Immunol.** 192, 52-58 (*: co-corresponding authors).

Fiala G, Rejas MT, Schamel WW, **van Santen HM** (2013). Visualization of TCR Nanoclusters via Immunogold Labeling, Freeze-Etching, and Surface Replication. **Methods in Cell Biology** 117, 391 - 410.

Bains I, **van Santen HM**, Seddon B, Yates AW (2013). Models of self-peptide sampling by developing T cells identify candidate mechanisms of thymic selection. **PLoS Computational Biology** 9 - 7, pp. e1003102.

Kumar R, Ferez M, Swamy M, Arechaga I, Rejas MT, Valpuesta JM, Schamel WW, Alarcon B*, **van Santen HM*** (2011). Increased Sensitivity of Antigen-Experienced T Cells through the Enrichment of Oligomeric T Cell Receptor Complexes. **Immunity** 35, 375-387 (*: co-corresponding authors).

Obst R, **van Santen HM**, Melamed R, Kamphorst AO, Benoist C, Mathis D. (2007). Sustained antigen presentation can promote an immunogenic T cell response, like dendritic cell activation. **Proc. Natl. Acad. Sci. USA** 104(39): 15460-15465.

Risueño RM, **van Santen HM**, and Alarcón B. (2006). A conformational change senses the strength of T cell receptor-ligand interaction during thymic selection. **Proc. Natl. Acad. Sci. USA** 103(25):9625-9630.

Schamel WW, Arechaga, I, Risueño RM, **van Santen HM**, Cabezas P, Risco C, Valpuesta JM, Alarcón B. (2005). Co-existence of multivalent and monovalent TCRs: a potential mechanism to explain high sensitivity and wide range of response. **J. Exp. Med.** 202(4):493-503.

Book chapters and reviews:

Alarcón B, **van Santen HM** (2016). T Cell Receptor Triggering. In: Ralph A Bradshaw and Philip D Stahl (Editors-in-Chief), Encyclopedia of Cell Biology, Vol 3, Functional Cell Biology, pp. 650-659. Waltham, MA: Academic Press; doi:10.1016/B978-0-12-394447-4.30097-9

Cuesta N, Martín-Cófreces NB, Murga C, **van Santen HM** (2011). Receptors, signaling networks, and disease. **Sci Signal.** 4(161):mr3.

Alarcón B, **van Santen HM**. (2010). Two receptors, two kinases, and T cell lineage determination. **Sci Signal.** 3(114):pe11.

Alarcón B, Swamy M, **van Santen HM**, and Schamel WWA (2006). T-cell antigen-receptor stoichiometry: pre-clustering for sensitivity. EMBO reports 7(5): 490-5.

C.2. Research projects and grants *(last 10 years)*

2017-2020: Desarrollo y comprobación preclínica de Receptores para Antígenos Quiméricos (CARs) bi-específicos contra la Leucemia Mieloide Aguda' (Development and preclinical testing of simultaneous dual engagement CARs (SiDECARs) against acute myeloid leukemia). PI: **HM van Santen**; funding agency: Fundación Ramón Areces; budget: €43.500.

2017 – 2021: European Network on Anti-Cancer Immuno-Therapy Improvement by modification of CAR and TCR Interactions and Nanoscale Geometry (EN-ACTI^{2}NG). Coordinator: **HM van Santen**, with participation of 12 groups and companies from Spain, Austria, Germany, The Netherlands and the United Kingdom; H2020-MSCA-ITN-2016, 721358; budget €2.539.859.

2017 - 2019: Investigacion de la señalizacion temprana por receptores para antigeno con fines terapeuticos. Co-PIs: B. Alarcón and **HM van Santen**; funding agency: Ministerio de Economía y Competitividad, plan estatal de investigación científica y técnica de innovación 2013-2016; ref.: SAF2016-76394-R; budget €380.000.

2014 - 2016: Manipulación de la organización de receptores de antígeno y sus señales tempranas para el tratamiento del cáncer y la autoinmunidad. Co-PIs: B. Alarcón and **HM van Santen**; funding agency: Ministerio de Economía y Competitividad, plan estatal de investigación científica y técnica de innovación 2013-2016; ref.:SAF2013-47975-R; budget €404.000.

2010 - 2012: Determinación del papel de GRK2 como coordinador de la diferenciación y migración timica. PI: **HM van Santen**; funding agency: Ministerio de Ciencia e Innovación, Plan Nacional de I+D+I; ref.: BFU:2009-08009; budget: €107.000.

2009: Análisis de la implicación de GRK2 en la diferenciación timica las células T. PI: **HM van Santen**; funding agency: Ministerio de Ciencia e Innovación, plan PIE; ref.: PIE:200820I171; budget: €30.000.

2006 – 2009: Mecanismos de señalización diferencial a través del complejo TCR-CD3 durante la selección timica. PI: **HM van Santen**; funding agency: Ministerio de Educación y Ciencia, Plan Nacional de I+D+I; ref.: BFU:2006-04031; budget: €93.000.

C.3. Contracts

Not applicable

C.4. Patents

Not applicable

C.5. Institutional responsibilities

2013 – present: coordinator seminars dept. of Cell Biology and Immunology, CBMSO
2013 – present: member electron microscopy committee CBMSO
2015 – present: member seminar committee CBMSO

C.6. Membership scientific societies

2013 – present: member 'Sociedad Española de Inmunología (SEI)'
2015 – present: member 'Sociedad de Inmunología Comunidad de Madrid (SICAM)'

C.7. Reviewing and evaluation activities

Reviewer for journals: Molecular Immunology, PLoS One, Human Immunology, BBA - Molecular Cell Research, Monoclonal Antibodies in Immunodiagnosis and Immunotherapy

Reviewer for grant agencies: ANEP, i-LINK CSIC, US-Israel Binational Science Foundation, Koningin Wilhelmina Fonds.