

Cover Page



Universiteit Leiden



The handle <http://hdl.handle.net/1887/33005> holds various files of this Leiden University dissertation

Author: Vos van Steenwijk, P.J. de

Title: Immunology and immunotherapy of high grade cervical lesions and cancer

Issue Date: 2015-05-19

LIST OF ABBREVIATIONS

ACT	Adoptive cell transfer
APC	Antigen-presenting cells
CD	cluster of differentiation
CIN	Cervical intraepithelial neoplasia
CTL	Cytotoxic T cells
CTLA-4	Cytotoxic T-Lymphocyte Antigen 4
CxCa	Cervical cancer
CXCL	chemokine (C-X-C motif) ligand
DC	Dendritic cells
E	Early antigen
GM-CSF	Granulocyte-macrophage colony-stimulating factor
HLA	human leukocyte antigen
HPV	Human papillomavirus
IDO	Indoleamine 2,3-dioxygenase
IFN	Interferon
IL	Interleukin
L1	Late antigen
LC	Langerhans cells
M1	Macrophage type 1
M2	Macrophage type 2
mAbs	Monoclonal antibodies
MICA	MHC class I chain related molecule A
NF- κ B	nuclear factor kappa-light-chain-enhancer of activated B cells
NK	Natural Killer
NKG2D	natural-killer group 2, member D
PD-1	Program death 1
PD-L	Program death ligand
PPR	Pathogen recognition receptor
SIL	Squamous intraepithelial lesions
SLP	Synthetic long-peptide
TAM	Tumour associated macrophages
TGF	Transforming growth factor
Th	T helper
TIL	Tumour infiltrating T cells
TIM	Tumour infiltrating myeloid cell
TIM-3	T cell immunoglobulin mucin-3
TLR	Toll-like receptor
TNF	Tumor Necrosis Factor
Treg	Regulatory T cells
UCHL1	Ubiquitin carboxyl-terminal hydrolase L1

AUTHOR AFFILIATIONS**From the Department of Clinical Oncology, LUMC**

Burg van der S. H.
 Doorduijn E.M.
 Goedemans R
 Ham van J.J
 Hall van T.
 Heusinkveld M.
 Hulst van der J.M.
 Loof N. M.
 Minne van der C. E.
 Piersma S.J.
 Ramwadhoebe T. H.
 Stynenbosch L. F. M.
 Welters M. J. P.

From the Department of Gynecology, LUMC

Berends-van der Meer D. M. A.
 Kenter G. G. (*Present Address: Center of Gynecologic Oncology Amsterdam*)
 Löwik M. J. G.
 Poelgeest van M. I. E.
 Vos van Steenwijk de P.J.

From the Department of Pathology, LUMC

Fleuren G. J.
 Gorter A.
 Jordanova E.S.
 Kuijjer M.L.
 Osse E. M.

From the Department of Clinical Pharmacology and Toxicology, LUMC

Fathers L. M.
 Oostendorp J.
 Valentijn A. R. P. M.

From the Department of Immunohaematology and Blood Transfusion

Melief C. J. M.

From the Department of Obstetrics and Gynecology, Haga Teaching Hospital, The Hague

Hellebrekers B. W. J.

From the Department of Obstetrics and Gynecology, Centrum Haaglanden, the Hague

Kagie M. J.
 Nooij L.

ISA Pharmaceuticals, Leiden
 Melief C. J. M.

ACKNOWLEDGEMENTS

A lot of people have contributed to this thesis to whom I owe many thanks. Clinical trials and translational research cannot be performed without optimal cooperation between departments and people. Building bridges between the laboratory and clinical practice is essential, challenging and inspiring.

With special thanks to:

Sjoerd van der Burg, for your fast mind, action and scientific wit. Your matter of fact way of thinking, your focus and dedication have taught me a lot. It is because of you I started this thesis and because of you I finished it.

Gemma Kenter, for creating the terms and conditions that have brought me where I am.

Mariëtte van Poelgeest, your passion and dedication to your patients, your precise way of working and perseverance are true examples to me.

Katja Jordanova, master of so many traits. Nothing is impossible for you, where there is a will there is a way.

D5 Clinical Oncology. A top team working together towards a communal goal for patients with cancer. The past years I have had the pleasure of being part of that team. I have learned so much from you and, for somebody who had to learn how to hold a pipette, there was a lot to learn. So many of you have contributed to the work in this thesis and all of you have contributed to a great time. It always feels a bit like coming home on the D5.

Tamara Ramwadhoebe, side by side we shared years of facsing, culturing, pulsing, ficolling, freezing, planning, Elispotting and LST-ing. Followed by even more time working out the results again and again..... and yes again! This thesis would not be without your help.

Margriet Löwik, Dorien Berends-van der Meer and Anneke Martins, without people like you there would be no clinical trial. Your commitment to the patients is fantastic.

Department of Pathology, for the invaluable contribution that *in vivo* work can bring and for all your help.

Ellen Hiemstra and Sabrina van den Tillaart for being great colleagues, for sharing laughter, frustration, scientific highs and lows. Edith van Esch, with whom I can share this crazy passion for immunotherapy. We have been through a lot together, hopefully we will continue

to do so in the future. All other colleagues of the Jay-seven and further, for all the scientific 'kroketten' lunches, meetings at Den Haspel and other 'conferences'.

My mother, how to thank someone who has given so much. You are the haven to which the ship can always return.

Egbert for giving me space to follow my heart, for trust, for humour, for family and most of all for love. As Kahlil Gibran wrote: the oak tree and the cypress grow not in each other's shadow.

And finally with thanks to Jaap, Martijn and Tygo without whom this book would probably have been finished a lot sooner.

CURRICULUM VITAE

Peggy Jacqueline de Vos van Steenwijk was born in Stamford USA on the 6th of March 1978. When she was one year old she moved with her family to Arnhem in the Netherlands. In 1982 the family went to live in France where Peggy attended the British School of Paris for four years after which she moved to Brussels, Belgium where she first attended the Prinses Juliana Dutch School and later the European School of Brussels, where she obtained the European Baccalaureate in 1996. Peggy chose to return to the Netherlands to study Medicine at the Erasmus University in Rotterdam where she completed her theoretical medical studies and then spent five months undertaking research at the Department of Surgery. Subsequently she spent six months working pro bono in a hospital in Tamil Nadu and travelling through India before returning to Rotterdam to complete her medical degree finishing with a final internship at the Queen Elisabeth Central Hospital in Blantyre, Malawi, Africa.

Peggy started work as an intern at the Bronovo Hospital in The Hague and left after one year to undertake research in Paris. She spent one and a half years at the Department of Clinical Immunology at the Institut Curie in Paris on a Mayer Rothschild Grant. Here she became interested in tumor immunology and started working on HPV induced pre-cancerous lesions and cervical cancer. Upon her return to the Netherlands in 2006 she began her training in Gynaecology at the Bronovo Hospital and the Leiden University Medical Center (LUMC). After she was awarded a ZonMW AGIKO grant, she committed to a 3 year PhD course at the Clinical Oncology and Gynaecology departments at the LUMC. Since then her work in clinical Gynaecology and PhD research have alternated each other.

Peggy lives in the Hague, is married to Egbert Huizing and they have three beautiful sons together Jaap, Martijn and Tygo.

LIST OF PUBLICATIONS

“Vaginal delivery under general anesthesia in a patient with massive pulmonary embolism.” de Vos van Steenwijk PJ, Nooij L, Arbous S, de Boer MA. *In preparation*

“The long-term immune response after HPV16 peptide vaccination in women with low-grade pre-malignant disorders of the uterine cervix: a placebo-controlled phase II study.” de Vos van Steenwijk PJ, van Poelgeest MI, Ramwadhoebe TH, Löwik MJ, Berends-van der Meer DM, van der Minne CE, Loof NM, Stynenbosch LF, Fathers LM, Valentijn AR, Oostendorp J, Osse EM, Fleuren GJ, Nooij L, Kagié MJ, Hellebrekers BW, Melief CJ, Welters MJ, van der Burg SH, Kenter GG. *Cancer Immunol Immunother.* 2014 Feb

“Tumor-infiltrating CD14-positive myeloid cells and CD8-positive T-cells prolong survival in patients with cervical carcinoma.” de Vos van Steenwijk PJ, Ramwadhoebe TH, Goedemans R, Doorduijn EM, van Ham JJ, Gorter A, van Hall T, Kuijjer ML, van Poelgeest MI, van der Burg SH, Jordanova ES. *Int J Cancer.* 2013 Dec

“A placebo-controlled randomized HPV16 synthetic long-peptide vaccination study in women with high-grade cervical squamous intraepithelial lesions.” de Vos van Steenwijk PJ, Ramwadhoebe TH, Löwik MJ, van der Minne CE, Berends-van der Meer DM, Fathers LM, Valentijn AR, Oostendorp J, Fleuren GJ, Hellebrekers BW, Welters MJ, van Poelgeest MI, Melief CJ, Kenter GG, van der Burg SH. *Cancer Immunol Immunother.* 2012 Sep

“M2 macrophages induced by prostaglandin E2 and IL-6 from cervical carcinoma are switched to activated M1 macrophages by CD4+ Th1 cells.” Heusinkveld M, de Vos van Steenwijk PJ, Goedemans R, Ramwadhoebe TH, Gorter A, Welters MJ, van Hall T, van der Burg SH. *J Immunol.* 2011 Aug

“Success or failure of vaccination for HPV16-positive vulvar lesions correlates with kinetics and phenotype of induced T-cell responses.” Welters MJ, Kenter GG, de Vos van Steenwijk PJ, Löwik MJ, Berends-van der Meer DM, Essahsah F, Stynenbosch LF, Vloon AP, Ramwadhoebe TH, Piersma SJ, van der Hulst JM, Valentijn AR, Fathers LM, Drijfhout JW, Franken KL, Oostendorp J, Fleuren GJ, Melief CJ, van der Burg SH. *Proc Natl Acad Sci U S A.* 2010 Jun

“An unexpectedly large polyclonal repertoire of HPV-specific T cells is poised for action in patients with cervical cancer.” de Vos van Steenwijk PJ, Heusinkveld M, Ramwadhoebe TH, Löwik MJ, van der Hulst JM, Goedemans R, Piersma SJ, Kenter GG, van der Burg SH. *Cancer Res.* 2010 Apr

“Surgery followed by persistence of high-grade squamous intraepithelial lesions is associated with the induction of a dysfunctional HPV16-specific T-cell response” de Vos van Steenwijk PJ, Piersma SJ, Welters MJ, van der Hulst JM, Fleuren G, Hellebrekers BW, Kenter GG, van der Burg SH. *Clin Cancer Res* 2008 Nov

“Mesh repair of postoperative abdominal wound dehiscence in the presence of infection” van’t Riet M, de Vos van Steenwijk PJ, Bonjer HJ, Steyerberg EW, Jeekel J. *Hernia*. 2007 Oct

“Incisional hernia after repair of wound dehiscence: incidence and risk factors” van’t Riet M, de Vos van Steenwijk PJ, Bonjer HJ, Steyerberg EW, Jeekel J. *Am Surg*. 2004

“The prevention of adhesions to a prosthetic mesh: comparison of different barriers using an incisional hernia model” van ‘t Riet M, de Vos van Steenwijk PJ, Bonthuis F, Marquet RL, Steyerberg EW, Jeekel J, Bonjer HJ. *Ann Surg*. 2003 Jan

“Tensile strength of mesh fixation in laparoscopic incisional hernia repair” van’t Riet M, de Vos van Steenwijk PJ, Kleinrensink GJ, Steyerberg EW, Bonjer HJ. *Surg Endosc*. 2002 Dec