Targeting MHC-I related proteins for cancer diagnosis and therapy

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List of abbreviations

ACT – Adoptive cell transfer
APC – Antigen presenting cell
BRCA1/2 – Breast cancer gene 1 / 2
CAR – Chimeric antigen receptor
CMV – Cytomegalovirus
CTL – Cytotoxic T lymphocyte
DAP-10 – DNAX-activating protein 10
DC – Dendritic cell
ECM – Extracellular matrix
EGF – Epidermal growth factor
EGFR – Epidermal growth factor receptor
ELISA – Enzyme-linked immunosorbent assay
EMT – Epithelial-to-mesenchymal transition
FACS – Fluorescence-activated cell sorting
GFB2 – Growth factor receptor bound protein 2
GFP – Green fluorescent protein
GrzB – Granzyme B
GVHD – Graft-versus-host disease
HcAb – Heavy chain-only antibody
HIV – Human immunodeficiency virus
HLA – Human leukocyte antigen
HPV – Human papillomavirus
IFN-γ – Interferon γ
Ig – Immunoglobulin
IL – Interleukin
ITAM – Immunoglobulin transactivation motif
ITIM – Immunoreceptor tyrosine-based inhibitory motif
KIR – Killer cell immunoglobulin-like receptor
LPS – Lipopolysaccharides
mAb – Monoclonal antibody
MAPK – Mitogen activated protein kinase
MHC – Major histocompatibility complex
MICA/B – MHC class I chain-related protein A/B
MYC – Myelocytomatosis oncogene
NFAT – Nuclear factor of activated T-cells
NFκB – Nuclear factor kappa-light-chain enhancer of activated B cells
NK cell – Natural killer cell
NKG2A/D – Natural killer group 2 member A/D
NKR – NK receptor
PBMC – Peripheral blood mononuclear cells
PI3K – Phosphoinositide 3-kinase
PTEN - Phosphatase and tensin homolog
RAS – Rat sarcoma virus
scFv – Single-chain variable fragment
SIV – Simian immunodeficiency virus
STAT3/5 – Signal transducer and activator of transcription 3/5
TAM – Tumor associated macrophage
Tcm – Central memory T cell
Tem – Effector memory T cell
TGF-β – Transforming growth factor-β
TME – Tumor microenvironment
Tfh cell – Follicular helper T cell
Th cell – T helper cell
TNF-α/β – Tumor necrosis factor α/β
Treg cell – Regulatory T cell
Tscm – Stem cell memory T cell
ULBP – UL-16 binding protein
VEGF – Vascular endothelial growth factor
VHH – Variable domain of HcAb
WCL – Whole cell lysate
WNT – Wingless-related integration site

Publications

Inge Ubink, **Elisha R. Verhaar**, Onno Kranenburg, and Roel Goldschmeding. A potential role for CCN2/CTGF in aggressive colorectal cancer. *Journal of Cell Communication and Signaling.* 2016;10(3). DOI: 10.1007/s12079-016-0347-5

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Novalia Pishesha, Thibault J. Harmand, Paul W. Rothlauf, Patrique Praest, Ryan K. Alexander, Renate van den Doel, Mariel J. Liebeskind, Maria A. Vakaki, Nicholas McCaul, Charlotte Wijne, **Elisha R. Verhaar**, William Pinney III, Hailey Heston, Louis-Marie Bloyet, Marjorie Cornejo Pontelli, Ma. Xenia G. Llagan, Robert Jan Lebbink, William J. Buchser, Emmanuel J. H. J. Wiertz, Sean P. J. Whelan, and Hidde L Ploegh. A class II MHC-targeted vaccine elicits immunity against SARS-CoV-2 and its variants. Proceedings of the National Academy of Sciences. 2021;118(44)e2116147118. DOI: 10.1073/pnas.2116147118

Arthur W. Lambert, Christopher Fiore, Yogesh Chutake, **Elisha R. Verhaar**, Patrick C. Strasser, Mei Wei Chen, Daneyal Farouq, Sunny Das, Xin Li, Elinor Ng Eaton, Yun Zhang, Joana Liu Donaher, Ian Engstrom, Ferenc Reinhardt, Bingbing Yuan, Sumeet Gupta, Bruce Wollison, Matthew Eaton, Brian Bierie, John Carulli, Eric R. Olson, Matthew G. Guenther, Robert A. Weinberg. ΔNp63/p73 drive metastatic colonization by controlling a regenerative epithelial stem cell program in quasi-mesenchymal cancer stem cells. *Developmental Cell.*2022;57(24):2414-2730.e8. DOI: 10.1016/j.devcel.2022.11.015

Elisha R. Verhaar, Anouk Knoflook, Novalia Pishesha, Xin Liu, Willemijn J.C. van Keizerswaard, Kai W. Wucherpfennig, Hidde L. Ploegh. MICA-specific nanobodies for diagnosis and immunotherapy of MICA$^+$ tumors. *Frontiers in Immunology.* 2024;15. DOI: 10.3389/fimmu.2024.13685586

Elisha R. Verhaar, Willemijn J.C. van Keizerswaard, Anouk Knoflook, Thomas Balligand, Hidde L. Ploegh. Nanobody-based CAR NK cells for possible immunotherapy of MICA$^+$ tumors. *PNAS Nexus*. 2024;5(3):pgae184 DOI: 10.1093/pnasnexus/pgae184

Elisha R. Verhaar, Jin Gan, Susan Buhl, Ziao Li, Amir Horowitz, Hidde L. Ploegh. A monoclonal antibody that recognizes a unique 13-residue epitope in the cytoplasmic tail of HLA-E. *Molecular Immunology.* 2024 article in press. Article reference: MIMM6935

Curriculum vitae

Elisha Verhaar is geboren op 17 januari, 1995 te Vlissingen. Zij behaalde haar VWO diploma aan het Dalton Lyceum in Barendrecht in 2013. In datzelfde jaar begon zij haar bachelorstudie “Biomedische Wetenschappen” aan de Universiteit Utrecht. Tijdens haar studie was ze actief bij meerdere studieverenigingen als hoofdredactrice van de redactie ter verenigingsblad “Tight Junction” der M.B.V. Mebiose, en theaterspecialist van de toneelcommissie “Produkcie”. Tijdens haar studie richtte ze zich op kanker- en stamcelonderzoek, onder meer met een onderzoeksstage in het UMC Utrecht naar de rol van connective tissue growth factor op de ontwikkeling van darmkanker, onder leiding van Onno Kranenburg en Roel Goldschmeding.

Na het behalen van haar bachelordiploma in 2016 startte ze aan de masterstudie “Cancer, Stem Cells, and Developmental Biology” aan de Universiteit Utrecht. Hier specialiseerde ze zich verder tot kankeronderzoek, onder meer met een stage aan het Hubrecht Instituut in het lab van Jacco van Rheenen, waar zij onderzoek deed naar celcompetitie in darmkanker organoids onder leiding van Saskia Suijkerbuijk. Hierna volgde ze een internationale stage in het lab van Robert Weinberg aan het MIT Whitehead Institute te Boston, Verenigde Staten. Onder leiding van Arthur Lambert deed zij onderzoek naar de rol van p63 en p73 op de epitheliale-naar-mesenchymale transitie van borstkankercellen.

Na het behalen van haar masterdiploma in 2018 werkte ze in de Weinberg groep aan hetzelfde project als onderzoeksassistent. In 2019 begon ze aan haar afstudeertraject in het lab van Hidde Ploegh, Boston Children’s Hospital, Verenigde Staten. In 2024 verdedigt ze haar proefschrift, en zal hierna waarschijnlijk werkzaam worden bij een biomedisch bedrijf in Boston, Verenigde Staten.

Acknowledgements

Beste Hidde, je gaf me alle vrijheid om zelf de teugels in handen te nemen maar stond altijd klaar om toch even een duwtje in de juiste richting te geven. Bedankt dat ik deze kans heb gekregen om mijzelf in jouw lab te ontwikkelen van "student" naar "wetenschapper".

Beste Sjaak, bedankt voor het accepteren van deze gekke PhD situatie. Hoewel we elkaar welgeteld drie keer gezien hebben, kan ik met zekerheid zeggen dat het Neefjes lab een fantastische plek moet zijn. Bedankt voor de adviezen en feedback op mijn werk.

Dear Thomas, thank you for entertaining me every single day, not just literally (your French swearing was entertaining!) You also entertained my many, many, many questions. I could always turn to you for help and advice about lab work, cloning, PET imaging, data analysis, medical problems, personal issues... The list goes on and on. I am not sure what I would've done without you in the bay. Cool bay forever!

Dear Lotte and Claire, together we were the "three PhD'ers". But we didn't just bond over mutual suffering, we made an actual connection. You girls are the best lab mates anyone could ask for. Dealing with all the "llama llama holiday drama" was easy with you guys thanks to our friendship. Always up for a drink, a hangout, a dance party (cue TomM!), raclette, board games, but also a serious chat or a vent. Thank you for becoming my friends.

Lieve Willemijn and Anouk, you both came to work with me like a gift from the UVA Heaven! Your dedication to the projects was unmatched and I can't even express how helpful the two of you have been. Your scientific mindset was a true inspiration to lift these projects to a higher level. You worked tirelessly on cloning vectors, creating virus, producing CAR NK and CAR T cells, designing and executing downstream applications, the list goes on... I am so lucky to have mentored you two incredible women and can't wait to see what your future holds.

Dear David, my liefje. You met me the month before I started my PhD and have dealt with the ups-and-downs of #PhDLife throughout the many years that followed. David, I can't emphasize enough how incredibly lucky I am to have you in my life and to be able to call you my husband. You have supported me in more ways than I could've ever hoped for. Not just by taking

over many of the household chores during my most busy times at work, but also by being there for me emotionally. You accepted when our plans had to change because I had to run experiments. You gave advice, even when I told you I wasn't looking for solutions. Liefje, you are always the solution. Coming home every day to yours and our cat's love, that's always been what's keeping me going.

Lieve papa. Wat zou ik graag willen dat je dit kon lezen... Ik weet hoe ontzettend trots je zou zijn geweest. Je vroeg zo vaak "en, ben je al bezig met het schrijven van je proefschrift?" en dan moest ik uitleggen dat ik nog steeds druk bezig was met experimenten, dus nee ik was nog niet aan het schrijven... Je stuurde me vaak linkjes naar interessante artikelen, en dan praatten we daar even over. Ik heb zo veel van jou geleerd en jij ook van mij. Hoewel jij nu niks meer van mij kunt leren, leer ik nog elke dag van jou. Papa, je meisje is nu echt klaar met haar proefschrift. Je had hem zo graag willen lezen. Ik draag hem op aan jou.

Lieve mama. Ik ben zo ontzettend blij dat ik dit moment met jou kan delen. Toen ik naar Boston verhuisde voor eens stage van 8 maanden zei je: "Meid, jij komt nooit meer terug naar Nederland". 'Onzin', dacht ik. Maar het is nu 6.5 jaar later en Boston is nog steeds mijn thuis. Ondanks de afstand hebben we elkaar zo vaak mogelijk gezien. Ik vind het zo bewonderingswaardig dat jij, zonder medische achtergrond, altijd zo geinteresseerd was in mijn onderwerp. Je wist altijd de juiste vragen te stellen waardoor we heerlijk konden kletsen over biomedische wetenschappen en mijn onderzoek. Mama, dank je wel voor de afgelopen jaren, voor het aanhoren van mijn frustraties, voor de altijd goede raad. Ik hou zo veel van jou.

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