



Universiteit  
Leiden  
The Netherlands

## **The power of help: mechanistic insights into CD4<sup>+</sup> T cell differentiation in vaccination and cancer**

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### **Citation**

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## Curriculum Vitae

Douwe Menno Tjebbe Bosma was born on January 24 1996, Rotterdam, The Netherlands. From 2008 to 2014, Douwe attended the Erasmiaans Gymnasium in Rotterdam, and completed his high-school education with profiles Nature & Health and Nature & Technology. Given that his main interests revolved around human biology, he started his Biomedical Sciences Bachelor studies at Utrecht University in 2014, and graduated in 2017. During his studies, he became interested in the interactions of the immune system with cancer and viruses. To pursue this interest, he enrolled in the Master's program Infection & Immunity of the Graduate School of Life Sciences at Utrecht University in 2017. During his Master's education, he performed an internship in the lab of Dr. Victor Peperzak at Utrecht University Medical Center, in which he aimed to enhance the cytotoxicity of genetically engineered T cells against cancer by using pro-apoptotic proteins. As writing assignment, he wrote a grant proposal on the role of the intestinal microbiome in generation of tissue-resident memory T cells under supervision of Prof. Dr. Derk Amsen at Sanquin. Subsequently, he moved to Zurich, Switzerland, where he studied the T cell response to Kaposi's sarcoma associated-herpesvirus and Epstein-Barr virus in humanized mouse models in the lab of Prof. Dr. Christian Münz. In 2019, he completed his Master's degree, and with his interests in T cell differentiation he joined the lab of Prof. Dr. Jannie Borst at Leiden University Medical Center as a PhD candidate. Since 2023 he is co-supervised by Dr. Fiamma Salerno. The results of this work are presented in this thesis.

## Portfolio

### Factual narrative of the PhD trajectory

Douwe began his PhD research project in October 2019, coinciding with the recent relocation of the research group of his supervisor and promotor Jannie Borst from the NKI to the LUMC. His first objective, together with Julia Busselaar, was to re-establish the murine *in vivo* DNA tattoo vaccination model at the animal facility of the LUMC. Initially, the No Help vaccine induced weak immune responses. Various strategies were tested to enhance CD8<sup>+</sup> T cell activation, including the use of the TLR agonist Aldara cream and vaccination with Herpesvirus synthetic long peptides. Over time, the No Help vaccine began to elicit stronger, more consistent responses, though still somewhat lower than those observed previously.

In early 2020, laboratory work was interrupted by the COVID-19 pandemic. During this period, Douwe dedicated his time at home to broadening his theoretical knowledge in immunology and on practical laboratory skills, particularly in flow cytometry, by following online courses, seminars, and workshops. When laboratory work resumed, he was among the first at the LUMC, and the first within his research group, to implement the new spectral flow cytometry systems. Throughout his PhD trajectory, Douwe developed, optimized, and validated several large spectral flow panels, including a myeloid/DC panel (used in Chapters 3 and 5), an in-depth CD4<sup>+</sup> T cell panel (Chapter 2), and a combined CD4<sup>+</sup>/CD8<sup>+</sup> T cell panel (Chapter 4). The DC panel was particularly instrumental for Elselien Frijlinks study on immune cell responses after radiotherapy (Chapter 5), for which Douwe provided extensive experimental support.

Using these tools, Douwe investigated the role of NK cells in CD8<sup>+</sup> T cell priming within the *in vivo* model. Although this project did not yield significant findings, it led to the observation of a specific expansion of MoDC populations in Help vaccination conditions, a finding that initiated the research described in Chapter 3. Parallel to this, Douwe collaborated with Julia Busselaar on the differentiation trajectory of CD8<sup>+</sup> T cells after DNA tattoo vaccination, resulting in Chapter 4.

During his work on CD4<sup>+</sup> T cell responses, Douwe recognized the lack of a reliable method to track antigen-specific CD4<sup>+</sup> T cells after DNA tattoo vaccination. To overcome this limitation, he acquired the PADRE tetramer and, together with Mo Staal, designed new DNA vaccines enabling the tracking of TCR transgenic OTII and SMARTA cells. These tools were validated and formed the foundation of the studies presented in Chapter 2. Together with Mo Staal, Douwe also designed and validated two transduced MC38 tumor cell lines that either expressed three identical PADRE epitopes or the

entire Help cassette, which was used in chapter 4 to study the effect of CD4<sup>+</sup> T cell epitope expression by tumors on CD8<sup>+</sup> T cell differentiation.

In 2022, Douwe supervised MSc student Mart de Boo, guiding the development of an *in vitro* DC–T cell priming platform. This platform was later adapted by Mo Staal to investigate how different cell death modalities influence DC–T cell communication. Although this work lies outside the scope of the present thesis, it has resulted in a manuscript regarding the method, and a manuscript on the experimental findings of the influence of cell death on DC function that are currently resubmitted and under revision, respectively.

That same year, Douwe contributed substantially to the application for a new CCD license for *in vivo* animal studies, an experience that provided valuable insight into ethical and regulatory processes. Following the arrival of Fiamma Salerno as a co-supervisor, Douwe's focus increasingly centered on CD4<sup>+</sup> T cell differentiation, which ultimately became his main research line and the core of Chapter 2, for which he also worked together with Julia Busselaar.

Douwe worked together closely with the mentioned members of the research group, but also shared his knowledge with other colleagues for experimental trouble shooting and trained new PhD students in murine experimentation. Overall, Douwe's PhD trajectory reflects both scientific and professional growth, and resulted in optimization of the key vaccination model, novel vaccine formulations, an adapted MC38 tumor model to study CD4<sup>+</sup> T cell differentiation in the context of cancer and flow cytometry strategies, as well as informative research findings that are published, or in the final stages of submission for publication.

## CRediT Table

CRediT table for the thesis of Douwe Bosma

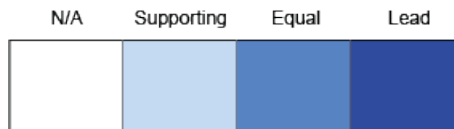
Ch.	Type*	Short Title	Conceptualization	Data Curation	Formal Analysis	Funding Acquisition	Investigation	Methodology	Project Administration	Resources	Software	Supervision	Validation	Visualization	Writing – Original Draft	Writing – Review & Editing	Preregistered	Preprinted	Published with Peer Review	
1	Introduction	General Introduction	Lead															<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2	PhD project chapter	Th1/Tfh precursor	Lead	Supporting	Supporting		Lead	Lead										<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3	PhD project chapter	CD4 T cell -MoDC feedback loop	Lead															<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
4	PhD project chapter	CD4 T cell help for CD8 T cells	Supporting	Supporting	Supporting		Lead	Lead										<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
5	Collaboration chapter	CD86 driven Treg response in RT							Supporting									<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
6	Discussion	General discussion	Lead															<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

\*PhD project chapters are the direct result of the PhD project of the PhD candidate. Some theses also include Collaboration Chapters, to which the PhD candidate has contributed but fall outside the PhD project.

Left to right colored:

Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – Original draft, Writing – Review and editing

Color scale:



Left to right ticked:

Preregistered, Preprinted, published with Peer Review

For more info, see; <https://osf.io/download/6845fa0e26e486cf1d539468/>



## List of publications

- 1. Mechanisms of action of PD-1 receptor/ligand targeted cancer immunotherapy.**  
Borst J, Busselaar J, Bosma DMT, Ossendorp F.  
Eur J Immunol. 2021 Aug;51(8):1911-1920. doi: 10.1002/eji.202048994. Epub 2021 Jun 21. PMID: 34106465
- 2. PD-1 or CTLA-4 blockade promotes CD86-driven Treg responses upon radiotherapy of lymphocyte-depleted cancer in mice**  
Frijlink E, Bosma DMT, Busselaar J, Battaglia TW, Staal MD, Verbrugge I, Borst J.  
J Clin Invest. 2024 Feb 13;134(6):e171154. doi: 10.1172/JCI171154. PMID: 38349740
- 3. KSHV infection of B cells primes protective T cell responses in humanized mice**  
Caduff N\*, Rieble L\*, Böni M, McHugh D, Roshan R, Miley W, Labo N, Barman S, Trivett, Bosma DMT, Rühl J, Goebels N, Whitby D, Münz C.  
Nat Commun. 2024 Jun 6;15(1):4841. doi: 10.1038/s41467-024-49209-w. PMID: 38844783
- 4. CD4<sup>+</sup> T-cell help delivery to monocyte-derived dendritic cells promotes effector differentiation of helper and cytotoxic T cells**  
Bosma DMT, Busselaar J, Staal MD, Frijlink E, Mack M, Salerno F#, Borst J#  
Immunol Lett. 2025 Apr 14:107022. doi: 10.1016/j.imlet.2025.107022. PMID: 40239818
- 5. Engineering anti-BCMA CAR T cells for enhancing myeloma killing efficacy via apoptosis regulation**  
Kimman T, Cuenca M, Slomp A, Tieland R, Rockx-Brouwer D, Heijhuurs S, Meringa AD, Boschloo W, Bosma DMT, Kroos S, Io Presto V, Nierkens S, Bovenschen N, Kuball J, Ovaa H, Minnema M, Sebestyén Z, Peperzak V  
Nat Commun. 2025 May 19;16(1):4638. doi: 10.1038/s41467-025-59818-8. PMID: 40389394

\*Shared First author

#Shared Last author

Included in this thesis; published articles #2, 4.

## List of submitted manuscripts

**1. Requirements for development of T-helper1 and T-follicular helper cells from a common precursor**

Bosma DMT\*, Busselaar J\*, Staal, MD, de Koning M, Lei X, de Wit T, Xiao Y, Borst J#\$, Salerno F#

Submitted to Cell Reports, in revision

Available on bioRxiv, <https://doi.org/10.1101/2025.09.08.674857>

**2. Stem-like PD-1<sup>+</sup>TCF-1<sup>+</sup> CD8<sup>+</sup> T cells result from helpless priming and rely on CD4<sup>+</sup> T-cell help to complete their cytotoxic effector differentiation**

Busselaar J\*, Bosma DMT\*, Staal MD, Lei X, Xiao Y, Borst J

Submitted to Journal for Immunotherapy of Cancer, in review

Available on bioRxiv, <https://doi.org/10.1101/2025.10.18.683204>

**3. Phagocytosis of necroptotic cells optimizes type 1 conventional dendritic cells for induction of a cytotoxic T-cell response**

Staal, MD, Wang Z, Bosma DMT, Busselaar J, de Vries E, Xiao Y and Borst J

Submitted to Cell Death and Differentiation, in revision

**4. Measuring in vitro induction of antigen-specific CD8<sup>+</sup> T-cell responses by murine conventional dendritic cells**

Staal MD, Bosma DMT, Borst J

Submitted to Methods in Cell Biology, in revision

\*Shared First author

#Shared Last author

\$Lead Contact

Included in this thesis; Submitted manuscripts #1, 2.

## Overview of completed courses and other training

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### Mandatory activities

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<i>Year</i>	<i>Title</i>	<i>Hours</i>
2018	Laboratory Animal Science	40
2020	Leiden University onboarding Programme Inform & Connect	5
2021	Basic methods and reasoning in biostatistics	32
2025	Conducting research in the LUMC	3

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### Scientific conferences, courses, workshops and other training activities

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<i>Year</i>	<i>Title</i>	<i>Hours</i>
2019	Dutch Society for Immunology (NVVI) winterschool (Noordwijk)	16
2020	MACS immuno-oncology day (Brussels, Belgium)	8
2020	NKI/LUMC Immunology symposium (Leiden)	8
2020	Webinar: Experimental Design and Considerations for Spectral Flow Cytometry	1
2020	Course Illustrator CC 2020 Masterclass (online)	40
2020	Global Immunotalks (online)	10
2020	NVVI Annual meeting (online)	16
2020	Oncode Annual meeting (Rotterdam)	16
2021	NVVI Lunteren symposium (online)	16
2021	Oncode Annual meeting (online)	16
2021	Webinar: OMIQ hands-on training	2
2021	European Congress of Immunology (online)	32
2021	NVVI Annual meeting (Noordwijk)	16
2022	Recent insights in immuno-oncology VIB (Leuven, Belgium)	16
2022	NVVI Winterschool (Noordwijk)	16
2023	16th ENII EFIS EJI Summer School on Advanced Immunology (Alghero, Italy)	21
2023	VIB European Macrophage and Dendritic Cell Society (Ghent, Belgium)	16

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**Presentations**


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<i>Year</i>	<i>Meeting</i>
2019-2024	<b>Speaker (occasionally):</b> Weekly department of Immunology (IMMU) meeting (Leiden)
2019-2024	<b>Speaker (occasionally):</b> Weekly Cancer Immunology (IMMU) meeting (Leiden)
2023	<b>Speaker:</b> 16th ENII EFIS EJI Summer School on Advanced Immunology (Alghero, Italy)
2023	<b>Poster:</b> 16th ENII EFIS EJI Summer School on Advanced Immunology (Alghero, Italy)
2023	<b>Poster:</b> IMMU Science Retreat (Leiden). <i>Awarded best poster presentation</i>
2024	<b>Speaker:</b> IMMU Science Retreat (Leiden).

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**Teaching**


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<i>Year</i>	<i>Title</i>	<i>Hours</i>
2022	Supervision of Mart de Boo, second year master student Life Science Technology at Leiden University	210

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## Acknowledgements

This thesis would not have been possible without the *Help* of so many people. During my PhD trajectory, I was fortunate to meet many inspiring, friendly and helpful people. It will be impossible to thank everyone in full in 800 words, but here we go;

First, I would like to thank my promotor Jannie for your help and guidance shaping me into the scientist I am today. Your support and dedication to bringing out the best version in your PhD students are truly remarkable, and I wish you all the best in the future and in your retirement.

My copromotor Fiamma, you have had such a massive influence on my PhD trajectory since you joined our team and without our scientific discussions, your input and help, this thesis would have looked very differently. You have everything to become a great group leader and I know you will have an amazing scientific career.

An enormous thanks to my paranims. Julia, what an amazing team we made. You are one of the smartest people I know and working together with you was a massive joy. Together, we were able to tackle the biggest experiments. And Mo, who would have thought that the person you sit next to in your first university lecture would be so important in your life. During our eleven year shared academic path our love for dry humor and 'van 9 tot 5', combined with your knowledge and perseverance have helped me a lot. To both of you, thank you for everything, and I wish you all the best for the future.

A massive thank you to all my TBI colleagues who helped me over the years. Elselien, thank you for all your advice, but mainly for all the fun we had. Who knew sharing FACS plots could become a life's business. Lotte, I really appreciated your energy, enthusiasm, and your openness to always grab a coffee when needed. Evert, I am quite sure the Hepathobar opens at 11. You always improved everyone's spirit. Ellen, you always show interest in everyone, which never went unnoticed. Mark, your friendliness, your enthusiasm and Treg expertise is massively appreciated. To Yanling, Xin, Tom and Sander, thank you for all the scientific advice, help and fun we had during social activities.

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