



Universiteit  
Leiden  
The Netherlands

## Novel mediators of anti-tumor immunity: dissecting intratumoral immune responses at the single-cell level

Vries, N.L. de

### Citation

Vries, N. L. de. (2022, October 6). *Novel mediators of anti-tumor immunity: dissecting intratumoral immune responses at the single-cell level*. Retrieved from <https://hdl.handle.net/1887/3439882>

Version: Publisher's Version

[Licence agreement concerning inclusion of doctoral thesis in the Institutional Repository of the University of Leiden](#)

License: <https://hdl.handle.net/1887/3439882>

**Note:** To cite this publication please use the final published version (if applicable).

# **Novel mediators of anti-tumor immunity: dissecting intratumoral immune responses at the single-cell level**

Natasja L. de Vries

Novel mediators of anti-tumor immunity:  
dissecting intratumoral immune responses at the single-cell level

ISBN: 9789464195460

Cover design by: Erik Heeres

Layout by: Ilse Modder | [www.ilsemodder.nl](http://www.ilsemodder.nl)

Printing by: Gildeprint Enschede | [www.gildeprint.nl](http://www.gildeprint.nl)

The research presented in this thesis was performed at the Department of Immunology and  
the Department of Pathology of Leiden University Medical Center in the Netherlands.

© 2022, Natasja L. de Vries, Amsterdam, the Netherlands

All rights reserved. No part of this thesis may be reproduced or transmitted in any form or  
by any means without prior written permission of the author.

**Novel mediators of anti-tumor immunity:  
dissecting intratumoral immune responses at the single-cell level**

Proefschrift

ter verkrijging van  
de graad van doctor aan de Universiteit Leiden,  
op gezag van rector magnificus prof.dr.ir. H. Bijl,  
volgens besluit van het college voor promoties  
te verdedigen op donderdag 6 oktober 2022  
klokke 11.15 uur

door

Natasja Lieuwke de Vries  
geboren te Leiden  
in 1992

**Promotor:** Prof.dr. F. Koning

**Co-promotor:** Dr. N.F.C.C. de Miranda

**Leden promotiecommissie:**

- Prof.dr. F.J.T. Staal
- Prof.dr. S.H. van der Burg
- Prof.dr. I.J.M. de Vries (Radboud UMC)
- Prof.dr. Z. Trajanoski (Medical University of Innsbruck)

"De adelaar zweeft graag hoog boven de wereld,  
niet om op de mensen neer te zien,  
maar om hen aan te sporen omhoog te kijken."

Uit: De cirkel van het leven, Kübler-Ross, E.

Ter nagedachtenis aan mijn moeder

Voor mijn ouders



# TABLE OF CONTENTS

<b>Chapter 1</b>	General introduction and outline of this thesis	13
<b>Chapter 2</b>	Unraveling the complexity of the cancer microenvironment with multidimensional genomic and cytometric technologies	27
<b>Chapter 3</b>	High-dimensional cytometric analysis of colorectal cancer reveals novel mediators of anti-tumor immunity	55
<b>Chapter 4</b>	$\gamma\delta$ T cells are effectors of immune checkpoint blockade in mismatch repair-deficient colon cancers with antigen presentation defects	91
<b>Chapter 5</b>	The ILC compartment in mismatch repair-deficient colorectal cancers is dominated by CD127-negative ILC1-like cells	135
<b>Chapter 6</b>	T cells with tumor-specific phenotypes largely originate from pericolic lymph nodes in colorectal cancer	167
<b>Chapter 7</b>	Local and systemic immune profiles of human pancreatic ductal adenocarcinoma revealed by single-cell mass cytometry	191
<b>Chapter 8</b>	General discussion and future perspectives	227
<b>Appendices</b>	Summary in English	238
	Nederlandse samenvatting	242
	Curriculum vitae and List of publications	250
	Acknowledgements / Dankwoord	254

## ABBREVIATIONS

B2M/β2m	β2-microglobulin
B2M <sup>KO</sup>	β2-microglobulin-knockout
B2M <sup>MUT</sup>	β2-microglobulin-mutant
B2M <sup>WT</sup>	β2-microglobulin-wildtype
BTN	Butyrophilin
CAR	Chimeric antigen receptor
CDR3	Third complementarity-determining region
CIN	Chromosomal instability
CM	Central memory
CML	Chronic myelogenous leukemia
COAD	Colon adenocarcinoma
CRC	Colorectal cancer
CyTOF	Cytometry by time-of-flight
DC	Dendritic cell
DRUP	Drug rediscovery protocol
EM	Effector memory
GMS	Gaussian mean shift
HLA	Human leukocyte antigen
HSNE	Hierarchical stochastic neighbor embedding
ICB	Immune checkpoint blockade
ILC	Innate lymphoid cell
IMC	Imaging mass cytometry
KIR	Killer-cell immunoglobulin-like receptor
LN	Lymph node
MHC	Major histocompatibility complex
MIBI-TOF	Multiplexed ion beam imaging by time-of-flight
MMR	Mismatch repair
MMR-d	Mismatch repair-deficient
MMR-p	Mismatch repair-proficient
MSI-H	Microsatellite instability-high
MSS	Microsatellite stable
NCR	Natural cytotoxicity receptor
PBMC	Peripheral blood mononuclear cell
PDAC	Pancreatic ductal adenocarcinoma
PDTO	Patient-derived tumor organoid
NK	Natural killer
scRNA-seq	single-cell RNA-sequencing
STAD	Stomach adenocarcinoma
TCR	T cell receptor
TCRβ	T cell receptor β-chain
TGF-β	Transforming growth factor-β

TIL	Tumor-infiltrating lymphocyte
TLS	Tertiary lymphoid structure
Treg	Regulatory T cell
t-SNE	t-distributed stochastic neighbor embedding
UCEC	Uterus corpus endometrium carcinoma
UMAP	Uniform manifold approximation and projection

