University of Groningen

Cellular and molecular immune markers of aging and frailty

Samson, Leon

DOI:
[10.33612/diss.178869624](https://doi.org/10.33612/diss.178869624)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2021

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):
Samson, L. (2021). *Cellular and molecular immune markers of aging and frailty*. [Thesis fully internal (DIV), University of Groningen]. University of Groningen. <https://doi.org/10.33612/diss.178869624>

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

CELLULAR AND
MOLECULAR IMMUNE
MARKERS OF AGING AND
FRAILITY

The investigations in this thesis were supported by the National Institute for Public Health and the Environment, the Netherlands.

This thesis was typeset using (R) Markdown, $\text{\LaTeX}$ and the **bookdown** R-package

ISBN: 978-94-6416-736-8

Printing: Ridderprint | www.ridderprint.nl

Cover design: Richard Dekker

An online version of this thesis is available at <https://www.publicatie-online.nl/publicaties/leon-samson>

© 2021 LD Samson

All rights reserved. No parts of this thesis may be reproduced, stored in a retrieval system or transmitted in any form by any means without the prior permission from the author, or when applicable, from the publishers of the scientific articles.

rijksuniversiteit
 groningen

Cellular and molecular immune markers of aging and frailty

Proefschrift

ter verkrijging van de graad van doctor aan de
 Rijksuniversiteit Groningen
 op gezag van de
 rector magnificus prof. dr. C. Wijmenga
 en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op

woensdag 1 september 2021, om 12.45 uur

door

Leonard Daniël Samson

geboren op 3 september 1986
 te Enschede

Promotores

Prof. dr. A.M.H. Boots

Prof. dr. W.M.M. Verschuren

Copromotores

Dr. P.M. Engelfriet

Dr. A.M. Buisman

Beoordelingscommissie

Prof. dr. P.E. Slagboom

Prof. dr. E. Brouwer

Prof. dr. A.W. Langerak

Paranimfen

Clothaire Spoto

Mary-lène de Zeeuw-Brouwer

Contents

1	General introduction	1
1.1	Aging population	2
1.2	Frailty and healthy aging	4
1.3	Importance of immune system in healthy aging	5
1.4	Aging-related changes in the immune system .	7
1.5	Missing knowledge	11
1.6	Research aim	11
1.7	Study cohort and study outline	12
1.8	Thesis outline	13
2	Frailty is associated with elevated CRP trajectories and higher numbers of neutrophils and monocytes	17
2.1	Introduction	19
2.2	Methods	20
2.3	Results	26
2.4	Discussion	36
2.5	Acknowledgements	40
3	In-depth immune cellular profiling reveals sex-specific associations with frailty	43
3.1	Introduction	46
3.2	Methods	47
3.3	Results	53
3.4	Discussion	61
3.5	Conclusions	67

3.6	Acknowledgements	67
4	The healthy aging index analyzed over 15 years in the general population: the Doetinchem Cohort Study	69
4.1	Introduction	71
4.2	Methods	72
4.3	Results	76
4.4	Discussion	82
4.5	Acknowledgements	86
5	Limited effect of duration of CMV infection on adaptive immunity and frailty: insights from a 27-year-long longitudinal study	89
5.1	Introduction	91
5.2	Methods	93
5.3	Results	98
5.4	Discussion	114
5.5	Acknowledgements	121
6	Relation of inflammatory marker trajectories with frailty and aging in a 20-year longitudinal study	123
6.1	Introduction	125
6.2	Results	126
6.3	Discussion	142
6.4	Methods	148
6.5	Acknowledgments	154
7	Impaired JAK-STAT pathway signaling in leukocytes of frail elderly	157
7.1	Introduction	159
7.2	Results	161
7.3	Discussion	172
7.4	Experimental procedures	176

8 General discussion	183
8.1 Summary of main findings	184
8.2 Challenges in aging research	186
8.3 Immunosenescence: where does it stand in the aging process?	187
8.4 Implications and future perspectives	197
8.5 Concluding remarks	202
 Appendices	 205
A Supplement to Chapter 2	207
B Supplement to Chapter 3	221
C Supplement to Chapter 4	243
D Supplement to Chapter 5	253
E Supplement to Chapter 6	259
F Supplement to Chapter 7	267
 Bibliography	 275
Nederlandse samenvatting (Summary in Dutch)	307
Dankwoord (Acknowledgements)	315