



Universiteit  
Leiden  
The Netherlands

## Unravelling the anti-carbamylated protein antibody response in rheumatoid arthritis

Verheul, M.K.

### Citation

Verheul, M. K. (2019, January 9). *Unravelling the anti-carbamylated protein antibody response in rheumatoid arthritis*. Retrieved from <https://hdl.handle.net/1887/68199>

Version: Not Applicable (or Unknown)

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

Downloaded from: <https://hdl.handle.net/1887/68199>

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

Cover Page



Universiteit Leiden



The handle <http://hdl.handle.net/1887/68199> holds various files of this Leiden University dissertation.

**Author:** Verheul, M.K.

**Title:** Unravelling the anti-carbamylated protein antibody response in rheumatoid arthritis

**Issue Date:** 2019-01-09

# Unravelling the anti-carbamylated protein antibody response in rheumatoid arthritis

Marije Klazina Verheul

Unravelling the anti-carbamylated protein antibody response in rheumatoid arthritis

ISBN                      9789463234573  
Printing                  Gildeprint

The research described in this thesis was carried out at the department of rheumatology, Leiden University Medical Center, Leiden, the Netherlands

Printing of this thesis was financially sponsored by Exagen Diagnostics and INOVA diagnostics

© Marije Verheul

# Unravelling the anti-carbamylated protein antibody response in rheumatoid arthritis

Proefschrift

Ter verkrijging van  
de graad van Doctor aan de Universiteit Leiden,  
op gezag van Rector Magnificus prof. mr. C.J.J.M. Stolker,  
volgens besluit van het College voor Promoties  
te verdedigen op woensdag 9 januari 2019  
klokke 15:00 uur

Door

**Marije Klazina Verheul**  
Geboren te Gouda  
1990

*Promotores*

Prof. Dr. R.E.M. Toes  
Prof. Dr. T.W.J. Huizinga

*Co-Promotor*

Dr. L.A. Trouw

*Promotiecommissie:*

Prof. Dr. A.H.M. van der Helm  
Dr. J. A. Bakker  
Prof. Dr. G.J.M. Pruijn (Radboud Universiteit, Nijmegen)  
Dr. D. Hamann (Sanquin, Amsterdam)



# Table of Contents

Chapter 1 – Introduction	9
<u>Part I - Clinical characteristics of anti-CarP antibodies</u>	
Chapter 2 – Biomarkers for rheumatoid and psoriatic arthritis	23
Chapter 3 – Anti-Carbamylated protein antibodies precede disease onset in monkeys with collagen-induced arthritis	41
Chapter 4 – Anti-Carbamylated protein antibodies in rheumatoid arthritis patients of Asian descent	53
Chapter 5 - Anti-carbamylated protein antibodies in the pre-symptomatic phase of rheumatoid arthritis, their relationship with multiple anti-citrulline peptide antibodies and association with radiological damage	59
Chapter 6 - Anti-Carbamylated Protein antibodies: a specific hallmark for rheumatoid arthritis - comparison to conditions known for enhanced carbamylation; renal failure, smoking and chronic inflammation	75
Chapter 7 - The combination of three autoantibodies, ACPA, RF and anti-CarP antibodies is highly specific for rheumatoid arthritis: implications for very early identification of individuals at risk to develop rheumatoid arthritis.	81



## Part II – Anti-CarP antibodies and their antigens

Chapter 8 - Pitfalls in the detection of citrullination and carbamylation 103

Chapter 9 – The identification of carbamylated alpha-1-antitrypsin (A<sub>1</sub>AT) as an antigenic target of anti-CarP antibodies in patients with rheumatoid arthritis 117

Chapter 10 – Mass spectrometric identification of carbamylated proteins present in the joints of RA patients and controls 135

Chapter 11 - Breach of autoreactive B-cell tolerance by post-translationally modified proteins 149

Chapter 12 – Discussion 167

## Part III – Addendum

Summary 180

Nederlandse Samenvatting 183

Curriculum Vitae 187

List of publications 191

Acknowledgements 193