



Universiteit
Leiden
The Netherlands

Marvellous ubiquitin : avenging the MERS-coronavirus papain-like protease

Knaap, R.C.M.

Citation

Knaap, R. C. M. (2020, February 12). *Marvellous ubiquitin : avenging the MERS-coronavirus papain-like protease*. Retrieved from <https://hdl.handle.net/1887/85167>

Version: Publisher's Version

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

Downloaded from: <https://hdl.handle.net/1887/85167>

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

Cover Page



Universiteit Leiden



The handle <http://hdl.handle.net/1887/85167> holds various files of this Leiden University dissertation.

Author: Knaap, R.C.M.

Title: Marvellous ubiquitin : avenging the MERS-coronavirus papain-like protease

Issue Date: 2020-02-12

**Marvellous ubiquitin:
avenging the MERS-coronavirus papain-like protease**

Robert Cornelis Martinus Knaap

COLOPHON

Marvellous ubiquitin: avenging the MERS-coronavirus papain-like protease

Robert C.M. Knaap

PhD thesis, Leiden University Medical Center, 2020

Cover design: Renate Holtrop

Layout & printing: Optima Grafische Communicatie

ISBN: 978-94-6361-389-7

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

Marvellous ubiquitin: avenging the MERS-coronavirus papain-like protease

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 12 februari 2020
klokke 16:15 uur

door

Robert Cornelis Martinus Knaap
geboren te Goes
in 1989

Promotor

Prof. dr. E.J. Snijder

Co-promotor

Dr. ir. M. Kikkert

Leden promotiecommissie

Prof. dr. D. van Baarle (Utrecht University)

Dr. P.P. Geurink

Prof. dr. R.C. Hoeben

Prof. dr. S. Perlman, MD (University of Iowa, USA)

A painting is finished when the artist says it is finished.
- statement attributed to Rembrandt van Rijn -

TABLE OF CONTENTS

Chapter 1 - General introduction	9
Chapter 2 - Crystal structure of the Middle East respiratory syndrome coronavirus papain-like protease bound to ubiquitin facilitates targeted disruption of deubiquitinating activity to demonstrate its role in innate immune suppression	27
Chapter 3 - The deubiquitinating activity of Middle East respiratory syndrome coronavirus papain-like protease delays the innate immune response and enhances virulence in a mouse model	53
Chapter 4 - Potent and selective inhibition of pathogenic viruses by engineered ubiquitin variants	81
Chapter 5 - Engineering improved ubiquitin variants that inhibit the papain-like protease of Middle East respiratory syndrome coronavirus	119
Chapter 6 - Structure and function of viral deubiquitinating enzymes	143
Chapter 7 - General discussion	171
References	199
List of abbreviations	227
Dutch summary	232
Curriculum vitae	236
List of publications	237