

University of Groningen

Oncolytic virotherapy - analysis, design, models

Bhatt, Darshak

DOI:
[10.33612/diss.859671389](https://doi.org/10.33612/diss.859671389)

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:
2024

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

Citation for published version (APA):

Bhatt, D. (2024). *Oncolytic virotherapy - analysis, design, models*. [Thesis fully internal (DIV), University of Groningen]. University of Groningen. <https://doi.org/10.33612/diss.859671389>

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.

ONCOLYTIC VIROTHERAPY

ANALYSIS, DESIGN, MODELS

DARSHAK BHATT

The research reported in this thesis was carried out as a collaboration between (1) the Tumor Virology and Cancer Immunotherapy lab, in the department of Medical Microbiology and Infection Prevention, of the University Medical Center Groningen and of the University of Groningen (The Netherlands), and (2) the Experimental Cancer Research lab, located in the Center for Translational Research in Oncology, Instituto do Câncer do Hospital das Clínicas, da Faculdade de Medicina da Universidade de São Paulo (Brazil). Part of the research was also carried out in collaboration with Theoretical Research in Evolutionary Life Sciences group (TRÊS), at the Groningen Institute for Evolutionary Life Sciences, of the University of Groningen, and SynBioNL - the Synthetic Biology association of the Netherlands.

Darshak Bhatt received a PhD scholarship from the Brazilian Federal Agency for Support and Evaluation of Graduate Education (CAPES) and the Graduate School of Medical Sciences in Groningen under the Abel Tasman Talent Program (GSMS-ATTP). The studies in this thesis were financially supported by a Scientific Research grant from the Stichting De Cock-Hadders and the São Paulo Research Foundation (FAPESP, grant Number 2020/09176-8).

Financial support for the printing of this thesis was kindly provided by the Graduate School of Medical Sciences at the University of Groningen.

Cover and layout: Darshak Bhatt

The cover features a genetically engineered virus at the center against the backdrop of a mosaic of cells organized within a tumor tissue.

Printed by: Ridderprint | www.ridderprint.nl

© 2024 by Darshak Bhatt. All rights reserved. No part of this publication may be used or reproduced by any means, without the permission of the author, or when appropriate, from the publishers of the papers.



university of
 groningen



ONCOLYTIC VIROTHERAPY - ANALYSIS, DESIGN, MODELS

PhD thesis

to obtain the degree of PhD at the
University of Groningen
on the authority of the
Rector Magnificus Prof. J.M.A. Scherpen
and in accordance with
the decision by the College of Deans

and

to obtain the degree of PhD at the
University of São Paulo
on the authority of the
Rector Magnificus Prof. C. G. Carlotti Jr.
and in accordance with the decision by
the decision by the Provost of Graduate Studies.

Double PhD degree

This thesis will be defended in public on
Wednesday, 24th January 2024 at 11 hours

by

Darshak Bhatt

born on 2 March 1995
in Dholka, India

Supervisors

Prof. C.A.H.H. Daemen
Prof. R. Chammas

Co-supervisor

Dr. C.I. Oyarce Díaz
Dr. L. Nogueira de Sousa Andrade

Assessment Committee

Prof. L.W. Seymour
Prof. J.D. Laman
Prof. G.P. Piljman
Prof. B.E. Strauss

Paranymphs

Luisa Hermann

Annemarie Boerma

BaukjeNynke Hoogeboom

To you, the reader

Index

<i>Chapter 1</i>	13
Introduction and outline of the thesis	
<i>Chapter 2</i>	41
A systematic analysis on the clinical safety and efficacy of onco-virotherapy	
<i>Chapter 3</i>	73
Oncolytic alphavirus replicons induce immune cell activation and recruitment towards human tumor cells and spheroids	
<i>Chapter 4</i>	105
Tumor-derived extracellular vesicles: modulation of cellular functional dynamics in tumor microenvironment and its clinical implications	
<i>Chapter 5</i>	123
Oncolytic alphavirus-induced extracellular vesicles counteract the immunosuppressive effect of melanoma-derived extracellular vesicles	
<i>Chapter 6</i>	149
Resistance mechanisms influencing oncolytic virotherapy, a systematic analysis	
<i>Chapter 7</i>	173
Modelling the spatial dynamics of oncolytic virotherapy in the presence of virus-resistant tumor cells	
<i>Chapter 8</i>	215
Modelling the effects of T cell mediated cytotoxicity on oncolytic virotherapy	
<i>Chapter 9</i>	247
A SynBio community comes of age: political, academical, industrial, and societal developments in The Netherlands	
<i>Chapter 10</i>	269
General discussion and future perspectives	
<i>Appendix</i>	
English summary	298

Nederlandse samenvatting	301
Resumo em Português	304
Acknowledgements	309
About the author	314

