

Into the blue...Using mouse models to uncover genes driving tumorigenesis and therapy resistance in human breast cancer Ruiter, J.R. de

Citation

Ruiter, J. R. de. (2019, May 22). Into the blue..Using mouse models to uncover genes driving tumorigenesis and therapy resistance in human breast cancer. Retrieved from https://hdl.handle.net/1887/73551

Version:Not Applicable (or Unknown)License:Leiden University Non-exclusive licenseDownloaded from:https://hdl.handle.net/1887/73551

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

Cover Page



Universiteit Leiden



The handle <u>http://hdl.handle.net/1887/73551</u> holds various files of this Leiden University dissertation.

Author: Ruiter, J.R. de Title: Into the blue...Using mouse models to uncover genes driving tumorigenesis and therapy resistance in human breast cancer Issue Date: 2019-05-22

Using mouse models to uncover genes driving tumorigenesis and therapy resistance in human breast cancer

Julian Rutger de Ruiter

About the cover:

Scuba diving is one of the major hobbies that my wonderful wife managed to impart on me. One thing that has always amazed me about diving is how many beautiful and complex interactions happen under the surface of the water, but sadly remain hidden to most of us. Even with our technological advancements, the majority of our ocean's depths are still a mystery — 'alien' worlds which remain to be explored. Personally, I feel that this reflects our current understanding of (cancer) cell biology, as we have learned much but are still only scratching the surface of the complex processes that occur within our cells. Fortunately, new technologies are providing us with more and more tools to venture out into the unknown 'deep blue', so that we may one day truly understand the underpinnings of our being.

Cover design: Julian R. de Ruiter Thesis layout: Julian R. de Ruiter Printed by: Gildeprint, Enschede ISBN: 978-94-6323-579-2

The layout design was based on the Clean Thesis style by Ricardo Langner. The cover photos were taken during the LSD 2018 Lustrum Diving Trip to Pico in the Azores.

The research described in this thesis was performed in the divisions of Molecular Pathology and Molecular Carcinogenesis of the Netherlands Cancer institute (Amsterdam, the Netherlands). Financial support was provided by the Netherlands Organization for Scientific Research (NWO: Cancer Genomics Netherlands) and the European Research Council (ERC Synergy project CombatCancer). The printing of this thesis was financially supported by the Netherlands Cancer Institute (Amsterdam, the Netherlands).

©Julian de Ruiter, 2019. All rights reserved. No part of this thesis may be reproduced, stored in a retrieval system, or transmitted in any form or by any means without prior permission of the author and the publisher holding the copyright of the articles.

Using mouse models to uncover genes driving tumorigenesis and therapy resistance in human breast cancer

Het gebruik van muismodellen om de sturende krachten achter tumor ontwikkeling en therapie resistentie in humane borstkanker te ontdekken

Proefschrift

Ter verkrijging van de graad van Doctor aan de Universiteit Leiden, op gezag van de Rector Magnificus prof.mr. C.J.J.M. Stolker, volgens besluit van het College voor Promoties, te verdedigen op woensdag 22 mei 2019 klokke 13:45 uur

> door Julian Rutger de Ruiter

Geboren te Farnborough, Groot Britannië in 1988

Promotor: Prof. dr. Jos Jonkers **Copromotor:** Prof. dr. Lodewyk Wessels

Promotiecommissie:

Prof. dr. Hubertus Irth (voorzitter)Prof. dr. Joke Bouwstra (secretaris)Prof. dr. Peter Devilee (Universiteit Leiden)Prof. dr. Bas van Steensel (Erasmus Universiteit)Dr. Jeroen de Ridder (UMC Utrecht)

1	Mouse models in the era of large human tumour sequencing studies	1
2	Scope of this thesis	33
3	Insertional mutagenesis identifies drivers of a novel oncogenic path- way in invasive lobular breast carcinoma	43
4	Identifying transposon insertions and their effects from RNA- sequencing data	105
5	Comparative oncogenomics and iterative mouse modeling identifies combinations of driver genes and drug targets in <i>BRCA1</i> -mutated breast cancer	149
6	Transcriptomics and transposon mutagenesis identify multiple <i>in vivo</i> mechanisms of resistance to the FGFR inhibitor AZD4547	189
7	Selective loss of PARG restores PARylation and counteracts PARP inhibitor-mediated synthetic lethality	229
8	General discussion	285
A	Appendices	301