Investigating possible bypass mechanisms to sensitize AML blasts for combination therapy
Kampen, Kim

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:
2015

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

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).

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.

Download date: 23-12-2018
Investigating possible bypass mechanisms to sensitize AML blasts for combination therapy

Targeting ligand induced receptor tyrosine kinase signaling

Proefschrift

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

De openbare verdediging zal plaatsvinden op
woensdag 16 september 2015 om 11.00 uur

door

Kim Rosalie Kampen

geboren op 15 juli 1985
te Oldehove
Promotor
Prof. dr. E.S.J.M. de Bont

Beoordelingscommissie
Prof. dr. E. Vellenga
Prof. dr. G.J.L. Kaspers
Prof. dr. S.M. Kornblau
Paranimfen
Frank Scherpen
HarmJan Lourens

This thesis

This PhD thesis covers the research performed to explore the dynamic adaptation potential of AML blasts. By investigating the opportunity of AML blasts to activate bypass mechanisms as escape routes that circumvent initial therapeutic targeting strategies, we identified frequent exploitation of RTK activation as initiation of cellular bypass mechanisms in pediatric AML. To this extend, we aimed to therapeutically interfere with the following ligand/receptor axis in AML e.g. VEGFC/VEGFR-2, NGF/TRKA, and EfnB1/EphB1.
Chapter 1. Hematopoiesis and the development of Leukemia................................. 7
  1.1 Introduction........................................................................................................ 8
  1.2 Genetic, molecular and epigenetic alterations in AML........................................ 9
  1.3 Cellular AML functions for disease maintenance............................................... 10
  1.4 Genetic interference with pathways for AML disease maintenance.................... 12
  1.5 Receptor Tyrosine kinases in AML ................................................................... 14
  1.6 Scope of this thesis............................................................................................ 15
Reference list ............................................................................................................. 18

Chapter 2. Vascular Endothelial Growth Factor signaling in Acute Myeloid Leukemia ...... 23
Abstract.................................................................................................................... 25
Introduction............................................................................................................... 26
VEGF-A, VEGF-C, VEGFR-2 and VEGFR-3 are overexpressed in AML....................... 27
VEGF-A and VEGF-C are adverse prognostic predictors in AML............................... 29
AML blast proliferation and survival is partially dependent on the VEGF/VEGFR signaling in subsets of AML patients ................................................................. 30
The role of VEGF in AML associated angiogenesis .................................................. 32
VEGF-A and VEGF-C; mediators of the endosteal and vascular stem cell niche ............ 34
VEGF targeted therapy in AML .............................................................................. 35
Summary and Future perspectives......................................................................... 40
Reference list ............................................................................................................. 41

Chapter 3. VEGFC targeted therapy reduces the CD34+ AML expansion by enhanced differentiation and apoptosis; A role for simultaneous glycolysis inhibition............ 47
Abstract.................................................................................................................... 49
Significance............................................................................................................... 50
Introduction............................................................................................................... 51
Materials & Methods.............................................................................................. 52
Results....................................................................................................................... 56
Discussion.................................................................................................................. 69
Acknowledgements................................................................................................. 71
Author contributions.............................................................................................. 71
Grant support........................................................................................................... 71