Advancing precision oncology: insights from C-terminal FGFR2/3 truncations and MYC-driven mTOR inhibitor resistance

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ADVANCING PRECISION ONCOLOGY

Insights from C-terminal FGFR2/3 truncations and MYC-driven mTOR inhibitor resistance

About the cover: The cover of this thesis symbolizes the wide spectrum of cancer patient identities, tumor types, and disease presentations encountered in oncology, represented by multiple abstract faces depicted in different colors. A subset of these faces is interconnected by lines, symbolizing shared genomic alterations that can range from single-nucleotide mutations to complex structural rearrangements. Although diverse in nature, such alterations may converge on common functional outcomes that drive tumor formation or therapy resistance. The ability to recognize these hidden molecular patterns relies on advanced next-generation sequencing technologies, robust computational and statistical frameworks, and the systematic functional validation of detected variants. Together, these approaches enable the identification of clinically meaningful alterations, including C-terminal truncations of *FGFR2* and *FGFR3*, as well as MYC activation associated with resistance to mTOR inhibitors, key discoveries explored throughout this thesis. By uncovering shared vulnerabilities among diverse tumors, this knowledge contributes to improved patient stratification and the development of more effective, individualized treatments, thereby advancing the goals of precision oncology.

Cover design: Sergio Vallés Martí | Instagram: @sergiarts
Thesis lay-out: Douwe Oppewal
Printing: Gildeprint Enschede | www.gildeprint.nl

ISBN: 978-94-6496-573-5

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Proefschrift

ter verkrijging van
de graad van doctor aan de Universiteit Leiden,
op gezag van rector magnificus prof.dr. S. de Rijcke,
volgens besluit van het college voor promoties
te verdedigen op dinsdag 22 september 2026
klokke 11:30 uur

door

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geboren te Sevastopol, Oekraïne
in 1993

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The research described in this thesis was performed at the division of Molecular Pathology at the Netherlands Cancer Institute – Antoni van Leeuwenhoek Hospital (NKI-AVL) (Amsterdam, The Netherlands). The research was financially supported by the Dutch Cancer Society and Oncode Institute.

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LIST OF ABBREVIATIONS

100kGP: 100,000 Genomes Project
3′-UTR: 3′-untranslated region
AACR: American Association for Cancer Research
ADCs: antibody–drug conjugates
AI: artificial intelligence
amp: amplification
AUC: area under the dose–response curve
AURKA: Aurora kinase A
BPs: breakpoints
CCA: cholangiocarcinoma
CC: coiled-coil
ChIP: chromatin immunoprecipitation
Chr-2: chromosome 2
CML: chronic myeloid leukemia
co-IP: co-immunoprecipitation
CR: complete response
C-tail: carboxy-terminal tail
ctDNA: circulating tumor DNA
E18: exon 18
EMA: European Medicines Agency
ER+: estrogen receptor–positive
ERK: extracellular signal–regulated kinase
FDA: U.S. Food and Drug Administration
FGF: fibroblast growth factor
FGFR: fibroblast growth factor receptor
***FGFR2*^{hotspot}:** *FGFR2* missense hotspot mutation
***FGFR2*$^{\Delta E18}$:** exon 18–truncated *FGFR2*
***FGFR3*$^{\Delta E18}$:** exon 18–truncated *FGFR3*
FGFRi: FGFR inhibitors
FL: full-length
FMI: Foundation Medicine Inc.
GDC: Genomic Data Commons
GEMMs: genetically engineered mouse models
GENIE: Genomics Evidence Neoplasia Information Exchange
GO: Gene Ontology
GSVA: gene set variation analysis
HER2: human epidermal growth factor receptor 2
HMF: Hartwig Medical Foundation
HR: hazard ratio

HSPG: heparan sulfate proteoglycan
I17: intron 17
iCCA: intrahepatic cholangiocarcinoma
IC50: half-maximal inhibitory concentration
ICI: immune checkpoint inhibitor
ICGC: International Cancer Genome Consortium
IGR: intergenic region
IHC: immunohistochemistry
ILC: invasive lobular carcinoma
IMD: IRSp53/MIM homology domain
JM: juxtamembrane domain
KD: kinase domain
KDBS: kinase domain–binding and suppression motif
KEP: *K14-Cre;Cdh1*$^{F/F}$*;Trp53*$^{F/F}$ mouse model
LC-WGS: low-coverage whole genome sequencing
LisH: lissencephaly-1-homology domain
LUAD: lung adenocarcinoma
LUSC: lung squamous cell carcinoma
mAbs: monoclonal antibodies
MAPK: mitogen-activated protein kinase
MS: mass spectrometry
MSI-H: microsatellite instability–high
mTOR: mechanistic target of rapamycin
mTORi: mTOR inhibitors
MYCi: MYC inhibitor
NGS: next-generation sequencing
NSCLC: non-small cell lung cancer
NXG: NOD-*Prkdcscid-IL2rgTm1*/Rj immunocompromised mice
OS: overall survival
PCAWG: Pan-Cancer Analysis of Whole Genomes
PDAC: pancreatic ductal adenocarcinoma
PDX: patient-derived xenograft
PFS: progression-free survival
PI3K: phosphoinositide 3-kinase
PI3Ki: PI3K inhibitors
PKC: protein kinase C
PR: partial response
RAF: rapidly accelerated fibrosarcoma
RAS: rat sarcoma
REs: rearrangements
Ribo-seq: ribosome profiling

RNA-seq: RNA sequencing
RPPA: reverse phase protein array profiling
RR: response rate
RTK: receptor tyrosine kinase
RT-qPCR: reverse transcription quantitative PCR
SB: Sleeping Beauty transposon system
SD: stable disease
siRNAs: small interfering RNAs
STAT: signal transducer and activator of transcription
TACC3: transforming acidic coiled-coil containing protein 3
TAM: tamoxifen
TCGA: The Cancer Genome Atlas
TEs: translation efficiencies
TF: transcription factor
TIDE: Tracking of Indels by Decomposition
TKI: tyrosine kinase inhibitor
TMB-H: tumor mutation burden–high
TMT: tandem mass tag
tRNA: transfer RNA
VUS: variants of unknown significance
WES: whole exome sequencing
WGS: whole genome sequencing
WGTS: whole genome and transcriptome sequencing
WT: wild-type