FACULTY OF MEDICINE AND HEALTH SCIENCES

Unravelling AKT2 Signalling in Cancer through Nanobody Technology

Tijs Merckaert

GHENT UNIVERSITY

VIB

Summary of the thesis

Protein Kinase B (AKT) is a central node in one of the most frequently dysregulated signalling pathways in human cancer, which makes this kinase a promising therapeutic target. However, AKT comes in three closely-related isoforms (AKT1, AKT2 and AKT3) that are non-redundant and can even have opposing functions. There is little consensus on which isoform should be targeted for cancer therapy, and there are no tools available that can inhibit a single AKT isoform.

The main goal of this thesis is to develop tools that can be used to interfere with a single AKT isoform in cells, to study isoform-specific signalling and validate AKT isoforms as a target for cancer therapy.

To achieve this, Nanobodies were generated for the AKT isoforms. After a stringent screening, where specificity for a single AKT isoform was the key criterion, AKT1- and AKT2-specific Nanobodies were obtained. Due to its role in promoting the metastasis of breast cancer cells, AKT2 became the main focus of the thesis. By using our AKT2 Nbs as a research tool we were able to map a part of AKT2's signalling cascade, strengthened AKT2 as a bona fide target for cancer therapy and established the importance of the hydrophobic motif for AKT2 signal transduction. These Nanobodies could aid in the rational design of an isoform-specific AKT2 inhibitor.

This thesis provides new tools that can be used to study AKT isoforms in cells, advocates the use of complementary techniques to study protein function and demonstrates the value of Nanobody technology as a research tool in fundamental research.

You are cordially invited to the public PhD defence of
Tijs Merckaert

Which will take place online on the
21st of April at **16h00 (GMT+1)**

At the following URL:
https://teams.microsoft.com/l/meetup-join/19%3ameeting_MWQ4MGE0ZjQtZTAwOS00MGVlLWJlZjItOTMzMWEwYmI5OGQ3%40thread.v2/0?context=%7b%22Tid%22%3a%22d7811cde-ecef-496c-8f91-a1786241b99c%22%2c%22Oid%22%3a%22f06f3bc8-23c0-492c-9220-20f808670a48%22%7d

Electronic version of the thesis

Ugent biblio or on request (see contact information)

Acknowledgements

This work was supported by an FWO PhD fellowship for Strategic Basic Research, VIB vzw, Ghent University and was conducted at the VIB-UGent Center for Medical Biotechnology and the UGent Department of Biomolecular Medicine, Faculty of Medicine and Health Sciences.

fwo Fonds Wetenschappelijk Onderzoek Vlaanderen
Opening new horizons

Promoters

Prof. Dr. Jan Gettemans[1]
Prof. Dr. Kris Gevaert[1,2]

Examination committee

Prof. Dr. Jolanda van Hengel[3]
Prof. Dr. Mark Rider[4]
Dr. Els Beghein[5]
Dr. Pieter Rondou[1]
Dr. Joni Van der Meulen[1]
Dr. Inna Afonina[6,7]

Affiliations

[1]Department of Biomolecular Medicine, Faculty of Medicine and Health Sciences, Ghent University, Ghent, Belgium

[2]VIB-UGent Center for Medical Biotechnology, VIB, Ghent, Belgium

[3]Medical Cell Biology Research Group, Department of Human Structure and Repair, Faculty of Medicine and Health Sciences, Ghent University, Ghent, Belgium

[4]Institut de Duve, Université catholique de Louvain, Brussels, Belgium

[5]Federal Agency for Medicines and Health Products, Brussels, Belgium

[6]Unit of Molecular Signal Transduction in Inflammation, VIB-UGent Center for Inflammation Research, VIB, Ghent, Belgium

[7]Department for Biomedical Molecular Biology, Ghent University, Ghent, Belgium

Key publications

Merckaert T, Zwaenepoel O, Gevaert K, Gettemans J. **Development and characterization of protein kinase B/AKT isoform-specific nanobodies**. PLoS ONE **15**:10 (2020).

Merckaert T, Zwaenepoel O, Gevaert K, Gettemans J. **An AKT2-specific nanobody that targets the hydrophobic motif induces cell cycle arrest, autophagy and loss of focal adhesions in MDA-MB-231 cells**. Biomedicine & Pharmacotherapy **133**:111055 (2021).

Curriculum vitae

2016-2021: PhD student (VIB-Ugent)

2013-2015: Master in Biomedical Sciences (Ugent)

2010-2013: Bachelor in Biomedical Sciences (Ugent)

CONTACT INFORMATION
Tijs.Merckaert@ugent.be
Nanobody Lab
UGent Department of Biomolecular Medicine
VIB-Ugent Center for Medical Biotechnology
www.ugent.be
www.cmb.vib.be

GHENT UNIVERSITY