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VRIJE UNIVERSITEIT BRUSSEL

PhD in Medical Sciences
2019-2020

INVITATION to the Public defence of

## Yana DEKEMPENEER

To obtain the academic degree of **'DOCTOR OF MEDICAL SCIENCES'**

# TARGETED ALPHA THERAPY WITH SINGLE-DOMAIN ANTIBODY FRAGMENTS, A NOVEL CANCER TREATMENT.

The defense will take place on Wednesday, 2nd September 2020 at 6 p.m.

and will be organised online

via Zoom meeting, accessible through the following link:

https://qf.vub.ac.be/redirects/PhD_defense_Yana_De_Kempeneer.php

and in Auditorium Piet Brouwer

**ADMITTANCE** to the auditorium will only be granted upon presentation of the personal invitation from the PhD candidate.

## Summary of the dissertation

The need for potent cancer treatments has paved the way for, amongst other exciting therapeutic strategies, a novel field of research that focusses on the specific - systemic - delivery of cytotoxic radiation to cancer cells, often referred to as targeted radionuclide therapy. In targeted radionuclide therapy, cytotoxic ionizing radiation is delivered to the tumor cells by attaching the source for radiation (radionuclides) to tumor-specific carrier molecules. In the case of disseminated or metastatic disease, with small cell clusters present throughout the body of a patient, α-particle emitting radionuclides might be well-suited because of their short path length and high linear energy transfer, which allows for the concentration of cytotoxic radiation to only a few cell diameters range. When properly bound to a targeting carrier, α-particle emitters have high tumor cell killing efficacies, while sparing healthy tissue.

A range of compounds have been described as targeting carriers in targeted α-particle therapy. In this thesis, single domain antibody fragments (sdAbs), derived from Camelid heavy-chain-only antibodies, are proposed as targeting carriers. SdAbs are attractive due to their small size, high specificity and binding affinity for their target and upon administration into preclinical tumor-bearing models, they exhibit a fast accumulation and homogeneous distribution in tumor tissue, while unbound radiolabeled sdAbs are cleared from the bloodstream very quickly. These characteristics match well with those of α-particle emitting radionuclides, as such the combination carries great potential to treat patients with difficult-to-treat metastasis. In this work, three different α-particle emitting radionuclides, namely astatine-211, bismuth-213 and actinium-225, were selected based on their physical characteristics, radiochemical ease of handling and finally their availability. All three were conjugated to the HER2-targeting sdAb using different chemical linkers. The three radiolabeled sdAbs were fully characterized in vitro and in vivo, in order to select the most optimal linker for further therapeutic evaluation. All radiolabeled HER2-targeting sdAbs resulted in a high tumor uptake in vivo and high tumor-to-background ratios. Finally, targeted alpha therapy with bismuth-213 and actinium-225 resulted in a significantly prolonged median survival of all treated mice. Overall, the results indicate that sdAbs are promising carriers for targeted alpha therapy and each radionuclide studied here has its own unique value. This innovative study paves the way to the development of new therapeutic approaches, not only for the treatment of HER2pos metastatic cancer, but also for the treatment of other types of cancer.

## Curriculum Vitae

Yana Dekempeneer was born on 28th of December 1992 in Leuven. She obtained her Master degree in Biomedical sciences with distinction in 2015 from the Katholieke Universiteit Leuven, Faculty of Medicine, Leuven. In October 2015, Yana started her PhD at the In Vivo Cellular and Molecular Imaging (ICMI) Laboratory, Research Cluster Imaging and Physical Sciences, Faculty of Medicine and Pharmacy at the Vrije Universiteit Brussel under the promotorship of Prof. Dr. Vicky Caveliers and Prof. Dr. Matthias D'Huyvetter. Here, Yana focused on the radiolabeling of the HER2-targeting single-domain antibody fragment with astatine-211: the optimization and the effect of different chemical linkers on their in vivo behavior, which resulted in her first research article published in Molecular Pharmaceutics. During this year, Yana spend 4 months as a research fellow at the Targeted Alpha Therapy Group at the University of Gothenborg (Sweden) under the supervision of Prof. Dr. Sture Lindegren. In October 2016, a joint PhD with the Radiochemistry expert group from the Nuclear Research Centre in Mol and the ICMI lab from the VUB was started to focus on the radiolabeling of the HER2-targeting single-domain antibody fragment with the short-lived radiometal bismuth-213. She cooperated with several national and international researchers during her PhD. Finally, a collaboration was initiated during her PhD with the Institute of Nuclear Chemistry and Technology in Warshaw for the evaluation of actinium-225 labeled sdAbs. Her work resulted in at least three first author publications in international peer-reviewed journals, along with 4 poster presentations and 7 oral presentations at national and international conferences. Yana was mentor of two master theses and received 1 best poster prize and one best oral presentation at two different national conferences.