FACULTEIT DIERGENEESKUNDE
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INVITATION PUBLIC DEFENSE

Targeting chitinase-like proteins to overcome immune checkpoint blockade resistance in heterogeneous triple-negative mammary tumors

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PROMOTORS
Prof. dr. Evelyne Meyer
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Curriculum Vitae

Robbe Salembier was born on May 26, 1998 in Kortrijk, Belgium. After obtaining his secondary school diploma in Modern Languages and Sciences at Sint-Aloysiuscollege in Menen, he began his studies in Biomedical Sciences at KU Leuven in 2016. He obtained his Master of Biomedical Sciences degree, specialization in Biomedical Basic and Translational Research, in 2022 with great distinction.

In November of that same year, he started as a doctoral researcher in the Department of Veterinary and Biosciences at the Faculty of Veterinary Medicine, Ghent University. His research was part of the three-year European TRANSCAN project on triple-negative breast cancer, entitled MAppinG adaptatioN Of tripLe negative breast cancer microenvironments to ImmunotherApy (MAGNOLIA).

Robbe Salembier is author and co-author of several peer-reviewed scientific publications, has presented his work at international conferences, and successfully completed the training program of the Doctoral Schools.

Where?

The defense will take place on
Friday January 16 2026 at 17.00h

Auditorium Hoogbouw (entrance 24 – third floor)
Faculty of Veterinary Medicine
Ghent University, Campus Merelbeke
Salisburylaan 133, Merelbeke

After the defense there will be a short reception

How to attend?

If you would like to attend, please register before January 8 2026, by email with subject “Attendance reception PhD” to robbe.salembier@UGent.be .

Members of the Jury

Prof. dr. Ward De Spiegelaere
Faculty of Veterinary Medicine, Ghent University
Chair

Prof. dr. Bert Devriendt
Faculty of Veterinary Medicine, Ghent University

Dr. Ine Lentacker
Faculty of Pharmaceutical Sciences, Ghent University

Prof. dr. Steven Van Laere
Faculty of Medicine and Health Sciences, University of Antwerp

Dr. Nicolaas Van Renne
Jules Bordet Institute, Université Libre de Bruxelles (ULB)

Summary

Triple-negative breast cancer (TNBC) is an aggressive BC subtype lacking estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) expression. It is commonly associated with high metastasis, early recurrence, and poor survival. Although immune checkpoint blockade (ICB), such as anti-programmed death (PD-1) and anti-PD-ligand (L)1, has improved TNBC outcome, most patients remain non-responsive due to marked tumor immune microenvironment (TIME) heterogeneity. This PhD therefore aimed to dissect mechanisms of ICB resistance and test strategies to reshape the TIME.

Chapter 1 outlines TNBC biology, the concept of a "hot" versus "cold" TIME (based on TIL abundance) and reviews TIME-directed therapies, highlighting the need for preclinical systems that capture immune diversity. **Chapter 2** defines three aims: (i) establish TNBC mouse models spanning TIME phenotypes, (ii) determine the role of chitinase 3-like 1 (CHI3L1) as an immunosuppressive driver of ICB resistance, and (iii) test whether blocking the broad chitinase-like protein (CLP) family (via chitin) further improves ICB. **Chapter 3** describes nine intraductal, immunocompetent mouse TNBC models that recapitulate human immune states. The 4T1-hot and 4T1-cold models—though mechanistically distinct—were both ICB refractory, with shared accumulation of suppressive myeloid cells, and were selected for further experimental work in the following chapter. **Chapter 4** shows that CHI3L1 is mainly derived from tumor-associated neutrophils (TANs) and drives the common myeloid-mediated suppression in both 4T1-based models. Moreover, CHI3L1 loss or antibody blockade reduced 4T1-hot and 4T1-cold tumor growth, decreased infiltration of TANs/myeloid-derived suppressor cells (MDSCs), and increased effector lymphocytes that led to sensitization of the 4T1 tumors to anti-PD-L1. **Chapter 5** demonstrates that chitin microparticles act as broad CLP blockers, suppressing tumor growth in the 4T1-hot- and similar 66CL4-based model more effectively than anti-CHI3L1 alone. When combined with anti-PD-1, chitin significantly improved anti-tumor immunity with reduced metastasis. **Chapter 6** integrates the PhD thesis findings, positioning CLP-targeting—especially chitin—as a promising adjunct to extend ICB benefit in TNBC and outlines future avenues for model refinement, testing of experimental therapeutics, development of alternative anti-CLP agents and identifying CHI3L1/CLPs as immunotherapeutic targets in other species.

Collectively, the experimental work presented in Chapters 3–5 provides a comprehensive preclinical framework for investigating TIME heterogeneity and therapeutic resistance in TNBC. The intraductal mouse models established in this thesis capture the full spectrum of "hot" and "cold" immune phenotypes observed in patients, serving as valuable platforms for mechanistic studies and drug testing. The identification of CHI3L1 as a key immunosuppressive factor and the demonstration of CLP-targeted strategies using chitin provide mechanistic insight into how remodelling the TIME can enhance ICB efficacy. Together, these studies advance the understanding of TNBC immunobiology and open new avenues for combinatorial therapies that integrate CLP inhibition with established immunotherapeutic regimens.