

# Short Curriculum Vitae

## 2023 - present Head of Production

GMP unit 3 (CellGenTherapies)

Ghent University Hospital

## 2017 – present Pre-doctoral research

Ghent University

## 2015-2027 Master of Science in Biomedical Sciences

Ghent University

## Access to the PhD thesis



## Thanks to

Bart & Karim, the Neo-mDC Team (Laurenz De Cock, Departments of Genetics, Thoracic oncology, GMP unit, study coordinators, Department of Pathology), the patients, members of lab BVDK and TTIL, VIB Proteomics and Sequencing core, members of the examination committee, colleagues of the first floor of MRB2, my family, my husband to be and my friends.



## Promoters

### Prof. Dr. Bart Vandekerckhove (MD)

Department of Diagnostic Sciences  
Ghent University, Belgium  
Department of Human Body Material  
Ghent University Hospital, Belgium

### Prof. Dr. Karim Vermaelen (MD)

Department of Internal Medicine and Pediatrics  
Ghent University, Belgium  
Department of Internal Medicine  
Ghent University Hospital, Belgium

## Members of the examination committee

### Prof. Dr. Piet Cools (Chair)

Department of Diagnostic Sciences  
Ghent University, Belgium

### Dr. Apr. Ine Lentacker (Secretary)

Department of Pharmaceutics  
Ghent University, Belgium

### Prof. Dr. Niek Sanders

Department of Veterinary and Biosciences  
Ghent University, Belgium

### Prof. Dr. Ir. Diether Lambrechts

Department of Human Genetics  
KU Leuven, Belgium  
Center for Cancer Biology  
VIB-KU Leuven, Belgium

### Prof. Dr. Wouter Scheper

Division of Molecular Oncology and Immunology  
The Netherlands Cancer Institute, Amsterdam

### Prof. Dr. Lieve Brochez (MD)

Department of Head and Skin  
Ghent University  
Department of Dermatology  
Ghent University Hospital



## DEVELOPMENT AND CLINICAL EVALUATION OF A DENDRITIC CELL VACCINE TARGETING PATIENT-INDIVIDUAL NEOANTIGENS IN LUNG CANCER

Joline Ingels

Public defense of Joline Ingels  
to obtain the degree of  
Doctor in Health Sciences  
2024-2025

# Summary

Immunotherapy in the form of immune checkpoint blockers (ICBs) has dramatically changed the therapeutic landscape of non-small cell lung cancer (NSCLC). Although some patients have long-term benefit from this therapy, the majority of NSCLC patients have no long-term clinical benefit. Several studies show that tumor mutational burden is correlated with a favourable response to ICB treatment in NSCLC patients. This is thought to be due, at least in part, to an increased presence of neoantigens presented on the surface of tumor cells to the T cells of our immune system. Neoantigens are small parts of mutated proteins that arise as a result of DNA damage (mutations) in the tumor. Neoantigens are mostly unique to a patient's tumor. **Vaccination against neoantigens is considered a promising and safe approach to increase the clinical response to ICBs in NSCLC patients.** Generation of a vaccine targeting patient-specific neoantigens starts with collection of tumor material of the patient, and continuous through sequencing, neoantigen candidate identification and finally on-demand manufacturing of a patient-specific, small vaccine batch.

The **Thoracic Tumor Immunology Lab** at Ghent University has recently **developed a therapeutic cancer vaccine based on dendritic cells (DCs)**, which are capable to drive T cell responses. To enable the DCs to drive neoantigen-specific T cell responses, the DCs are loaded with messenger RNA (mRNA) encoding patient-specific neoantigens. At Ghent University, a collaboration was set up with several research groups, including my host laboratory, **to leverage this DC-based vaccine, which we call Neo-mDC, in the clinic for the treatment of NSCLC patients. The ultimate goal of the clinical trial trajectory is to combine Neo-mDC vaccination with ICB treatment in metastatic NSCLC patients**, who represent the majority of NSCLC cases at diagnosis and have a high medical need.

In this PhD, **we first successfully developed a process that meets GMP requirements for the production of small batches of neoantigen-coding mRNA.** The mRNA production process was validated in our GMP facility by performing three consecutive production runs and subjecting the resulting mRNA batches to quality controls. This validation study showed that the process delivers mRNA batches with consistent high quality.

**We then evaluated the Neo-mDC vaccine for the first time in a clinical trial in NSCLC patients, with the main aim of conducting an in-depth study of T cell immunity elicited by the Neo-mDC vaccine.** Vaccine generation was successful in six out of 10 recruited patients. The vaccine was well tolerated, with no serious side effects. In five of the six vaccinated patients, we could demonstrate vaccine-induced T-cell responses in the blood. These responses were already detectable after the first dose and remained detectable for at least 19 months after the last dose. The vaccine-induced T-cell population showed an almost complete differentiation spectrum, including T cell states associated with long-term immunity. Moreover, the vaccine-responsive T-cell population was found to be polyclonal, with different clonotypes showing different stages of differentiation. Three of the six vaccinated patients relapsed during the two-year follow-up period. In summary, these results demonstrate that Neo-mDC vaccination is safe, feasible and capable of inducing long-lasting, polyclonal T cell responses with a high degree of differentiation heterogeneity, thus providing a multifaceted T cell response.

In the course of this PhD, we witnessed the COVID-19 pandemic, which accelerated the breakthrough of vaccine technology based on lipid particles packaging mRNA (called nanoparticles). This technology is now increasingly being used in the development of therapeutic cancer vaccines. In contrast, interest in mDC-based vaccines has declined

significantly in recent years. In the final part of this thesis, we discuss why further development of mDC vaccines may still be valuable. In addition, we discuss the challenges we will face if we want to translate the Neo-mDC vaccine approach to advanced NSCLC patients. In conclusion, **this PhD work lays the foundation for further clinical development of the Neo-mDC vaccine in combination with ICB treatment in patients with metastatic NSCLC.**

## Publications

Ingels J, De Cock L, et al. Neoantigen-targeted dendritic cell vaccination in lung cancer patients induces long-lived T cells exhibiting the full differentiation spectrum. *Cell Reports Medicine* 2024.

Ingels J, et al. Small-scale manufacturing of neoantigen-encoding messenger RNA for early-phase clinical trials. *Cytotherapy* 2022.

## Funding

Bijzonder Onderzoeksfonds (UGent), Kom op Tegen Kanker

