Short Curriculum Vitae

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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

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GHENT UNIVERSITY

FACULTY OF MEDICINE AND HEALTH SCIENCES

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
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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, called 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 important 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 as combinatorial partner for 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.

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