FACULTEIT DIERGENEESKUNDE
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GHENT UNIVERSITY

LABORATORY OF GENE THERAPY

INVITATION
PUBLIC DEFENSE
Self-amplifying mRNA platforms for durable expression of therapeutic payloads

VERVAEKE PIETER
August 19, 2025 – 17h30

PROMOTERS
Prof. dr. Apr. Niek N. Sanders
Faculty of Veterinary Medicine, UGent
dr. Francis Combes
SINTEF

Curriculum Vitae

Pieter Vervaeke was born on September 26, 1996, in Mouscron. In 2020, he obtained a Master's degree in Veterinary Medicine with highest distinction from Ghent University. During his studies, he completed a voluntary summer internship in "Anesthesia and Surgery" as part of the Faculty of Veterinary Medicine's Top Student Program. Fascinated by advanced therapeutic platforms, Pieter subsequently began his doctoral research at the Laboratory for Gene Therapy in the Department of Veterinary and Biosciences at the Faculty of Veterinary Medicine, Ghent University. This study was funded by the Research Foundation – Flanders (FWO) as well as Ghent University. In addition to his research, Pieter completed training in “Valorization, Technology Transfer, and IP Protection” and the “Researchpreneurship” bootcamp. To further develop the research line of his doctorate, he contributed to securing an IOF StarTT grant. Finally, in 2025, Pieter obtained the Doctoral Degree in Veterinary Sciences.

Pieter Vervaeke is the author or co-author of three scientific publications and reports, with a fourth publication in preparation. A part of the scientific results have also been patented. Pieter has presented at several conferences and received the “Best Pitch Award” for one of his presentations.

Where?

The defense takes place on:
Tuesday, August 19, at 17h30.

Auditorium D (entrance 19)
Faculty of Veterinary Medicine
Ghent University, Campus Merelbeke
Salisburylaan 133, Merelbeke

The defense is followed by a short reception.

Registration

If you wish to attend the reception, please register before August 10, 2025, via pieter.vervaek@ugent.be

Members of the Jury

Prof. dr. Mathias Devreese
Chair of the Jury
Faculty of Veterinary Medicine, UGent

Prof. dr. Katrien Remaut
Faculty of Veterinary Medicine, UGent

Prof. dr. Koen Breyne
Massachusetts General Hospital, Harvard Medical School

Prof. dr. Jolien Van Cleemput
Faculty of Veterinary Medicine, UGent

Prof. dr. Luk Vandenberhge
Harvard Medical School

Summary

The discovery of mRNA in the 1960s marked the beginning of a series of scientific developments that would lead to life-altering outcomes for virtually every living person today, as illustrated by the millions of lives saved through COVID-19 mRNA vaccines.

While the progress made with mRNA vaccines has been remarkable, the promise of mRNA as a therapeutic platform to treat virtually any protein-based condition has yet to be fully realized. One of the key underlying challenges is the lack of durability, as conventional mRNA typically ceases protein expression within one to two days. Since it is unlikely that improvements to conventional mRNA will drastically extend its duration of action, we directed our efforts toward a more advanced platform: self-amplifying mRNA (SAM). SAM can replicate itself after administration, allowing the production of a therapeutic protein for 4 to 8 weeks.

The main objectives of this study were to investigate the requirements for the non-clinical development of mRNA as a therapeutic agent, as well as to explore various strategies for optimizing SAM as a platform for durable expression of therapeutic proteins.

In the first chapter, we mapped the regulatory landscape concerning the biodistribution of advanced therapies such as mRNA during non-clinical development. To our surprise, we discovered that, at the time of writing, the applicable regulatory guidelines either did not apply to mRNA, made no mention of RNA-based therapies, or lacked universally accepted definitions. We subsequently identified that commonly used techniques for non-clinical biodistribution studies are not always ideally suited for mRNA. Therefore, we proposed a range of alternative techniques that could be considered, such as RT-qPCR, in vivo fluorescence, and in vivo bioluminescence. We concluded that a shift from a product-specific approach to more general guidelines may become necessary as the number of (m)RNA therapies seeking clinical approval continues to grow rapidly.

In the second chapter, we examined the performance of four novel responsive SAMs. In these SAMs, translation of the gene of interest (GOI) can be switched off by administering the small-molecule compound trimethoprim (TMP). This provides control over the duration and intensity of protein expression following SAM administration. In this study, we demonstrated that the new responsive SAMs either exhibit higher expression in the “on” state or lower expression in the “off” state. In addition, we showed that one of the new SAMs responds rapidly to switching on or off. We concluded this part of the research by introducing a mechanistic model and proposing further improvements to the responsive SAM platform.

In the third chapter, we explored structural modifications to SAM that resulted in altered protein expression kinetics. We found that SAMs can be engineered to produce the same total amount of protein but at a slower rate. Moreover, we observed that this slower rate was associated with significantly improved cellular health. Based on these characteristics, the structurally modified SAMs were referred to as “enhanced SAM” (eSAM). In further research, we extensively mapped the improved cellular health as well as the altered kinetics. We developed a high-throughput screening platform to identify which structural modifications led to the desired effects, and which had no or undesired effects. Finally, we demonstrated that protein expression following intramuscular injection of eSAM could last up to 5 months, compared to 4–8 weeks with conventional SAM.