Personal note

My journey through my PhD was quite an adventure. Imagine, just a few months into working in the PPOL lab, I decided to take a leap across the big pond to New York and join MSK. A young PhD student, suddenly living alone for the first time, in a completely different country! It was a bit nerve-wracking at first, but quickly, the stress melted away, and I found myself exploring and growing in this new place. During my time there, I was a Ghent PhD student working in a stem cell lab in NYC, officially part of two other labs, and collaborating with a third. While this sounds, and at times was, a bit complicated, it allowed me to experience different environments and collaborate with a diverse group of scientists. So I want to thank my mentors Frank, Stephen, Katleen, and Liselot for guiding and supporting me, giving me the incredible opportunity to work abroad, and weather through the crazy times like the COVID lockdowns.

To my friends and family, thank you for always having my back and all the fun times. As meeting new people in New York isn't always easy, I want to especially thank you, Luz, for dragging me to happy hours, get-togethers, and exploring the city together. Most importantly, for introducing me to the woman who would later become my wife.

Finally, to my Cita, Schattebout, your enduring love, unwavering support, and infinite patience have meant the world to me. Your support is my strength, and I can't wait for the next chapter of our lives together!

Lots of hugs,

Stéphane

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Human pluripotent stem cell modeling, from normal development to neuroblastoma

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Summary

Understanding how human nerve cells develop and the disruptions they face is essential for tackling nerve-related disorders, especially neuroblastoma (NB), the most common solid tumor in children outside the brain. Recreating real-life development in the lab has been a challenge. In order to improve our ability to investigate this process we developed a model to mimic sympathetic nerve cell development. We verified that our lab-grown cells closely resemble the complexities of real human development, providing a unique insight into nerve cell intricacies. This sets a strong foundation for future research into both normal and abnormal nerve cell development.

To demonstrate our approach, we used our model to study how a common genetic change (ALKR1275Q) seen in familial NB affects normal development. Our findings revealed a specific group of cells with increased SOX2 expression, a factor linked to maintaining an early cell state. We think this genetic change might disrupt normal development in these cells, making them more susceptible to further mutations. Additionally, we explored what happens when we increase the activity of the MYCN gene during a specific developmental phase. This led to a wave of cell death, especially in certain cell types. The surviving cells showed signs of cancer-like behavior, such as avoiding cell death and rapidly growing, while keeping their developmental identity. Further tests in mice confirmed these cells could form tumors, with variations depending on when MYCN was activated. These discoveries deepen our understanding of how MYCN contributes to NB development, pointing towards new possibilities for treatments.

The full version of the dissertation is available online at:
https://biblio.ugent.be

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Publications in this thesis

Human iPSC modeling recapitulates in vivo sympathoadrenal development and reveals an aberrant developmental subpopulation in familial neuroblastoma.
Stéphane Van Haver, *et al.,* iScience, 2023

MYCN overexpression biases human sympatho-adrenergic development towards progenitor cells causing neuroblastoma-like tumor xenografts.
Stéphane Van Haver, et al., Submitted in Science Advances, 2023

Publications not included in this thesis

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