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Targeting for success: mechanistic insights into microRNA-based gene therapy for Huntington disease

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Stellingen behoren bij het proefschrift:

“Targeting for success: Mechanistic insights into microRNA-based gene therapy for Huntington disease”

1. Gene-silencing therapeutics for Huntington disease should not only target the complete mutant huntingtin protein but also the toxic exon-1 containing fragments to achieve therapeutic efficacy. (*this thesis*)
2. Secreted AAV-delivered therapeutic microRNAs can be used as translational pharmacokinetic biomarkers to monitor durability of microRNA-based gene therapy in brain diseases. (*this thesis*)
3. We propose a novel mechanism of dissemination of engineered miRNA therapeutics mediated by extracellular vesicles, termed “cross-corrective silencing”. Cross-corrective silencing contributes to the widespread distribution and efficacy of a promising AAV-mediated miRNA-based gene therapy for Huntington disease. (*this thesis*)
4. One-time local infusion of AAV-miHTT is sufficient for widespread and enduring expression of therapeutic miRNAs in the affected brain areas of large animals. (*this thesis*)
5. The development of disease biomarkers is the most important element to achieve effective treatments and personalized medicine for brain diseases. Disease biomarkers will contribute to drug development by facilitating early diagnosis and prognosis, stratification of patients and monitoring treatment response.
6. “Understanding the central biological mechanisms that underlie ageing is important for identifying novel therapeutic targets for neurodegenerative diseases.” Azam et al. 2021. *Front. Cell Dev. Biol.*
7. Delivery of gene therapies to diseased brain cells is one of the major challenges for the treatment of neurodegenerative diseases. The solution will come from non-invasive delivery methods that, by mimicking biological processes, can track down the location and dissemination of toxic molecules.
8. Translation of preclinical data to patients will greatly improve thanks to the combination of biodistribution studies in large animals and the mechanistic insights from novel patient-derived cellular models.
9. Some of the greatest advances in science were made by scientists that ventured outside of their original field of knowledge and know-how. Therefore, it is essential to connect with and learn from other disciplines to spark novel ideas.
10. “*I have not failed. I have just found 2,000 ways not to make a lightbulb*” - Thomas A. Edison. This quote reminds me that lack of therapeutic efficacy in clinical studies can actually increase our knowledge on how to develop better therapeutic solutions.
11. “*Success is a journey, not a destination*” - Arthur Ashe. Success (in science) is the result of moving in different directions, creating and connecting different paths, approaching a goal from different perspectives instead of pointing with an arrow and moving into a single direction. Success is keeping the journey of learning ongoing.