Developing antisense oligonucleotides for Huntington disease and spinocerebellar ataxia type 3: exon skipping as a therapeutic strategy in polyglutamine diseases

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Stellingen behorende bij het proefschrift getiteld

Developing Antisense Oligonucleotides for Huntington Disease and Spinocerebellar Ataxia Type 3:
Exon Skipping as a Therapeutic Strategy in Polyglutamine Diseases

1. The overlap between HD-related biological processes detected in YAC128 mice and HD patients confirms the value of this mouse model. (this thesis)
2. The beneficial effects of AON-mediated exon skipping on molecular outcomes and behaviour of HD and SCA3 mice show the potential of these treatments. (this thesis)
3. Although often neglected, including a control group treated with scrambled AON is essential to distinguish non-specific AON-effects from specific AON-effects. (this thesis)
4. Further investigating the effect of exposing the brain to AON compounds, regardless of their sequence, will be crucial to better predict adverse events seen in the clinic. While doing so, differences between healthy and diseased brains should be taken into account. (this thesis)
5. Despite the challenge of separating noise from true results, short-read RNA sequencing can be used to compare the toxicity of AONs and prioritize off-target splicing events for further research. (this thesis)
6. The shortcomings of in silico prediction of AON-induced splicing events underscore gaps in our understanding of splicing and demonstrate the need to study AON off-target effects empirically. (this thesis)
7. Understanding and improving the preclinical pipeline of drug development is required to increase the success rates of drugs in clinical trials.
8. A major hurdle in studying the effect of treatment is the difficulty to detect and monitor disease, especially for early-stage intervention, emphasizing the need for reliable biomarkers.
9. The key point in the timing of treatment for polyglutamine diseases remains the tradeoff between the occurrence of potentially irreversible effects without treatment and decades of treatment to people without any discomfort in life. Based on: Bachoud-Lévi AC. The Lancet Neurology. 2020;19(6):473-475.
10. In the set-up of a study involving laboratory animals, not only the well-being of the animals but also the well-being of the researcher should be taken into account in order to let the study succeed.
11. A scientific system that promotes and rewards collaboration more would benefit research into rare, complex diseases.
12. The value of pipet tips increases when you have to count them.