Developing an antisense oligonucleotide treatment for Spinocerebellar Ataxia Type 3

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Stellingen

Behorend bij het proefschrift:

Developing an antisense oligonucleotide treatment for Spinocerebellar Ataxia Type 3

1. Spinocerebellar ataxia type 3 is the result of sustained exposure to the mutant ataxin-3 protein. Once a therapy alleviating mutant ataxin-3 toxicity becomes available, pre-symptomatic treatment of patients is therefore the best treatment strategy. *(this thesis)*

2. Due to their monogenetic nature, polyglutamine disorders are ideal candidates to benefit from promising new gene therapies. *(this thesis)*

3. Using antisense oligonucleotide mediated exon skipping, ataxin-3 can be truncated to lack the toxic polyQ repeat and still retain its ubiquitin binding and cleavage function. *(this thesis)*

4. The fact that a mouse model expressing the human mutant ataxin-3 gene develops only molecular SCA3 hallmarks without ataxic symptoms during its 2-year lifespan argues for its scientific validity, rather than against it. *(this thesis)*

5. Knocking out ataxin-3 is tolerated in mice without obvious symptoms. However, until the first healthy human subject lacking ataxin-3 is identified, it is best to avoid complete downregulation of (wild-type) ataxin-3 when pursuing therapeutic strategies. *(this thesis)*

6. "Their presence in many wild-type proteins across a variety of species is intriguing and suggests that normal polyQ tracts might have a function. The fact that some organisms have orthologs lacking the polyQ tract indicates that the protein can fulfil its tasks without this feature: its function cannot be essential." *(M. H. Schaefer, E. E. Wanker, M.A. Andrade-Navarro, Nucleic Acids. Res., 2012)*

7. "Rich datasets can extend the spectrum of possible findings and permissible conclusions about the brain. Yet, the unavoidable impact on data analysis practices is currently shunned." (*D. Bzdok & B.T. Thomas Yeo, hal-01356923, 2016)*

8. "Chasing after the workings of the brain is not like chasing after the Higgs boson, where everyone goes after the same single target. It is about the community setting goals in a deliberate manner and working towards them in a disciplined manner." *(P. Mitra, Nature, 2013)*

9. "The intention of orphan drug legislation in the United States and Europe is to make the development of drugs for orphan diseases profitable. The unintended consequence is exploitation of the rules for profit." (*R.E. Ferner & D.A. Hughes, BMJ, 2010)*

10. "De weg naar nieuwe wetenschappelijke inzichten is geplaveid met teleurstelling, onvermogen en botte pech." *(H. Dijstelbloem, F. Huisman, F. Miedema, W. Mijnhardt, Science in Transition, 2013)*

11. De notie "tijd is geld", zou in de academische wereld meer toegepast moeten worden.

12. De grootste wetenschappelijke doorbraken zijn niet terug te vinden in de oorspronkelijke grant aanvraag, maar worden onvoorzien gedaan tijdens de uitvoering.