Splice modulation therapy for inherited retinal diseases

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Statement of the Problem: Inherited retinal diseases (IRDs) are characterized by severe and progressive visual impairment, often leading to complete blindness. IRDs display a tremendous genetic and clinical heterogeneity, and to date, no effective treatment exists. A significant fraction of the genetic defects underlying IRD affect pre-mRNA splicing of the corresponding gene. We therefore decided to employ antisense oligonucleotides (AONs) to develop splice modulation therapy for specific genetic subtypes of IRD. AONs are small and versatile DNA/RNA molecules that bind complementary to their target pre-mRNA molecule and are able to redirect pre-mRNA splicing.

Methodology & Theoretical Orientation: Fibroblast cell lines derived from patients harboring mutations that affect pre-mRNA splicing were generated and cultured in the presence of AONs that are specifically designed to correct pre-mRNA splicing. In some cases, fibroblasts were first reprogrammed to induced pluripotent stem cells that were subsequently differentiated to photoreceptor precursor cells, and then treated with AONs. RT-PCR analysis was performed to study the efficacy of AON treatment, and for some cell lines, Western blot analysis or immunocytochemical analysis was performed to determine the effects at the protein and cellular level.

Findings: AON administration to patient-derived fibroblast cells harboring a recurrent splice mutation underlying severe early-onset IRD, i.e. c.2991+1655A>G in CEP290, resulted in full restoration of CEP290 pre-mRNA splicing, a significant increase in CEP290 protein levels, and rescue of a ciliary defect. In addition, AON delivery to patient cells with splice mutations in ABCA4 resulted in correction of the splice defects. Studies targeting additional mutations affecting pre-mRNA splicing that underlie IRD are currently ongoing.

Conclusion & Significance: Splice modulation therapies represent a promising and attractive strategy for the future treatment of specific genetic subtypes of IRD.

Biography
Rob W J Collin is an Associate Professor at the Department of Human Genetics, at the Radboud University Medical Center in Nijmegen, The Netherlands, and is affiliated to the Donders Institute for Brain, Cognition and Behaviour. During his Post-doc, he was involved in the identification of several novel genes underlying inherited hearing impairment, and inherited retinal diseases. From 2010, he switched his research focus towards the development of Molecular Therapies for Inherited Eye Disorders, in particular those that involve the modulation of pre-mRNA splicing. In 2010, he worked in the lab of Prof. Dr. Jean Bennett, a pioneer in the development of retinal gene therapy. He was awarded with a prestigious VENI Award from the Dutch Organization of Scientific Research (2010), an Individual Investigator Award from the Foundation Fighting Blindness (2012), and recently received the IJMS Young Investigator Award (2017).

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