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Gene therapy of Stargardt disease with AAV intein vectors

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Our group has a long-standing interest in the development of gene therapies for inherited ocular diseases. Our research spans from tailoring the adeno-associated viral (AAV) vector platform to retinal gene transfer to proof-of-concept in animal models of retinal disease up to first-in-human. Indeed, we have importantly contributed to the phase I/II clinical trial of Luxturna, which is the first ocular gene therapy product on the market.

One of the limitations of AAV is its DNA cargo capacity of about 5 kb in size. This would not be sufficient for gene therapy of conditions like Stargardt disease (STGD1), the most common inherited macular degeneration in humans, which is caused by mutations in ABCA4, a gene with a coding sequence significantly larger than 5 kb.

To overcome this, we have recently developed a system based on two AAV vectors, each encoding for one of the two halves of ABCA4 each flanked by short split-inteins which mediate protein trans-splicing and full length ABCA4 reconstitution in the retina of mice, pigs and in human retinal organoids. This system reduces lipofuscin accumulation in a mouse model of STGD1 and supports further development of AAV intein for therapy of STGD1 and other Inherited Retinal Diseases (IRDs) due to mutations in large genes.

The overall objective of the project funded by Arrigo Recordati International Prize for Scientific Research is to translate this proof-of-concept of pre-clinical efficacy of AAV split intein for STGD1 into a first-in-humans by defining both AAV intein dose-response and safety in view of a future clinical trial. This will importantly contribute to the development of gene therapy for the common and severe STGD1.