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Autore	TORNABENE, PATRIZIA
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Sommario	Retinal gene therapy with adeno-associated viral (AAV) vectors is safe and effective yet it is limited by AAV cargo capacity of about 5 kb. AAV transfer capacity which is expanded by dual AAV up to 9 kb would still not suffice for treatment of inherited retinal diseases, such as Alström syndrome type I (ALMS) due to mutations in ALMS1 (CDS: 12.5 kb). For this purpose, I have generated triple AAV vectors, with a maximal transfer capacity of about 14 kb, encoding for ALMS1. Full-length protein expression occurs both in vitro and in the mouse retina where around 4% of photoreceptors are transduced by triple AAV vectors. ALMS1 showed correct localization in the mouse retina and this results in improvement of the retinal phenotype of a mouse model of ALMS. Additionally, I propose a different strategy to reconstitute large proteins in the retina which is protein trans-splicing mediated by split-inteins. Here I show that delivery of multiple AAV vectors each encoding for one of the fragments of either EGFP or large therapeutic protein flanked by short split-inteins results in full-length protein reconstitution in the retina of mice, pigs and in human retinal organoids. Moreover, the levels of large protein reconstitution achieved improves the retinal phenotype in a mouse model of Leber congenital amaurosis type 10 due to mutation in CEP290. These data support the use of split-

	inteins-mediated protein trans-splicing in combination with AAV subretinal delivery for gene therapy of inherited blindness due to mutations in large genes.
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