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Subretinal Delivery of EIAV-based Lentiviral Vectors in the Shaker1 mouse model for Usher Syndrome Type 1B : Development of UshStat®

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Usher syndrome type 1B is a combined deaf-blindness condition caused by mutations in the *MYO7A* gene. The loss of function of Myo7A protein in the RPE and photoreceptors leads to blindness. We have evaluated the impact of subretinally delivered UshStat®, a recombinant minimal equine infectious anaemia virus- (EIAV) based vector expressing human *MYO7A*, on photoreceptor function in response to different light intensities in *shaker1* mice, a mouse model of Usher type 1 B. Subretinal injections of EIAV CMV GFP or EIAV CMV MYO7A (UshStat®) were performed in *shaker1* mice. Photoreceptor function in EIAV CMV MYO7A treated eyes was determined histologically by evaluating alpha-transducin translocation in photoreceptors in response to low and high light levels. In addition, the neuroprotection from photoreceptor degeneration in response to chronic light intensity was evaluated. Subretinal delivery of EIAV vectors in the mouse lead to gene transfer and expression in photoreceptors and RPE cells. In the *shaker1* mouse model lacking functional Myo7A, subretinal delivery of the UshStat® protected photoreceptors from intense light damage as indicated by reduced photoreceptor cell loss and restored threshold for translocation of alpha-transducin in the photoreceptors. UshStat® tolerability in the macaque following the subretinal injection is ongoing. We have shown that subretinal delivery of UshStat® is able to restore the alpha-transducin translocation phenotype in the *shaker1* mouse model and neuroprotect the photoreceptors from high light intensity damage. These data support the development of an EIAV-based gene replacement therapy to treat Usher type 1B syndrome.

Biography

Dominic Cosgrove received his Ph.D. in Biochemistry from University of Nebraska Medical Center in 1989 and did his post-doc at the Faculte de Medicine (CNRS) in Strasbourg France. He has been the director of the gene expression laboratory at BTNRH since 1991. His research interests focus on defining the molecular mechanisms of Usher syndrome and Alport syndrome.