Ruslan N. Grishanin et al., J Clin Exp Ophthalmol 2014, 4:5
http://dx.doi.org/10.4172/2155-9570.S1.017

OMICS Group Conferences
Accelerating Scientific Discovery

4th International Conference on
Clinical & Experimental Ophthalmology
July 14-16, 2014 DoubleTree by Hilton Baltimore-BWI Airport, USA

Adeno-associated virus-mediated delivery of amyloid β antibody for treatment of age-related retinal degenerative diseases

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Geriatric retinal-degenerative diseases such as age-related macular degeneration (AMD) and glaucoma share certain pathological features with Alzheimer's disease (AD) including accumulation of extracellular deposits containing amyloid β (Aβ) peptides. Immunotherapy targeting the Aβ is being investigated as a potential treatment for the treatment of AMD and glaucoma. In this study we assessed the feasibility of the viral delivery of humanized therapeutic Aβ antibody to the retinal pigmented epithelium and retinal cells, for the continuous production of the anti-Aβ antibody in the eye in preclinical animal models.

Methods: RN6G is a humanized monoclonal antibody that recognizes both Aβ40 and Aβ42 species associated with pathology, but not the non-pathogenic amyloid precursor protein (APP). For viral delivery, RN6G was engineered as monocistronic cassette with a 2A self-cleavage linker sequence between the heavy and light antibody chains. This antibody expression cassette was delivered to retina in mice using a recombinant AAV vector. The vector was injected either subretinally, or intravitreally into C57B6 mice.

Results: Analysis of tissue distribution and pharmacokinetics indicated that antibody expression was limited to a subpopulation of cells in the ganglion cell layer following intravitreal delivery. In contrast, after subretinal delivery, full length and pharmacologically active RN6G was stably expressed in the retinal pigment epithelium (RPE). Intraocular levels of antibody were significantly higher than serum levels. Intraretinal expression of RN6G did not impair retinal function measured by electroretinogram.

Conclusion: Full length therapeutic anti-Aβ IgG engineered as a monocistronic cassette with 2A self-cleavage site can be successfully delivered to retina via rAAV vector. Since complete IgGs are stable molecules with low immunogenicity, this technology allows the investigation of targeting Aβ in retinal degenerative diseases in animal models. Furthermore, the technology may provide a way for the continuous delivery of therapeutic antibodies to treat chronic retinal degenerative diseases, if proven safe and effective in humans.

Biography

Ruslan Grishanin has completed his Ph.D. in biochemistry from Moscow State University, Russia. His postdoctoral research was focused on molecular mechanisms of exocytosis in neurons and endocrine cells and role of BDNF through TrkB signaling in the development of retinal architecture and function. In 2008 he joined Pfizer, where he led efforts in the development of treatment for age related macular degeneration, neuroprotection strategy for glaucoma, as well as in the design of novel cancer immunotherapy.

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