

Unique Insight of Retina Gene Therapy

Tina Guanting Qiu*

Ophthalmic Physician Executive, Ophthalmic Therapeutic Innovation, USA

***Corresponding Author:** Tina Guanting Qiu, Ophthalmic Physician Executive, Ophthalmic Therapeutic Innovation, USA.

Received: January 05, 2018; **Published:** January 08, 2018

2017 is an exciting year made a landmark in gene therapy. Spark Therapeutics received FDA advisory committee approval of hRPE65 gene therapy for patients with LCA2 (Lebers Congenital Amaurosis) [1]. It took 20-year winded journey to establish a viable clinical regulatory path forward, during which period gene therapy paradigm has evolved from classic gene replacement to using genetic engineer as drug delivery tool and optogenetics to address various stages of neurovascular problems in the retina. The youngest birth is CRISPR-based gene editing technology, which is dancing on a new wave of precision medicine. With overarching new technologies across broad disciplines, things will move faster with better results. There are a few important subjects that are underappreciated which could stumble the field.

First, we need to know who is your close neighbor (tissue): brain or heart? Like Alzheimer's, Parkinson's and Huntington's diseases, inherited retina degeneration (IRD) is of neural degenerative disorder and has cross-talk with the brain and neuroscience. To improve and maintain photoreceptor/RPE health and survival has strategic importance for enhancing gene transfer efficiency and long-term visual benefits. Although Luxturna (AAV2-hRPE65v2) is marked as one-time lifelong treatment for LCA2, there are evidences suggesting that gene replacement therapy via subretina injection may only provide a short term clinical effect because the treatment can only rescue a small area (bleb) of the retina cells where the genetic constitute is being transfected [2]. As the degenerative disease progresses toward advanced stage, these rescued photoreceptor/RPE cells may eventually die off due to overwhelming dead cell signals rising from adjacent non-treated retina neurons that are speedily undergoing apoptosis and/or necrosis. For example, the Phase 2 clinical study of subretina delivery of rAAV-REP1 gene for choroideremia (n = 6 patients) showed a trend of the visual acuity declined during the first 3.5 year follow up [2]. Due to the surgical challenge performed on a terminally ill and thin retina tissue, the maximal volume for single subretina injection can only go up to 1000 uL that covers up to 1/3 of the retina [3], however current recommended volume by Spark trial surgeons and several others is 300uL, with which the bleb size can only cover ~1/5 of the retina [1]. The constrains of the bleb size set a practical limit for improving pan-retina visual sensitivity, and renders a technical challenge to early-stage disease intervention to rescue fovea vision for example in the case of retinitis pigmentosa.

Notably, in hRPE65-LCA2 clinical trials, patients received bilateral treatments have a better vision improvement compared to those who only received one injection [1]. Why? In drug development, we do see therapeutic benefits in non-treated fellow eye if one eye is being dosed via intraocular route [4]. Anatomically, there are two short-cut circulating routes that may facilitate molecules, antibodies or viral vectors traveling from one eye directly to the fellow eye without going through the entire systemic circulation. The first route exits from vortex vein in the choroid → ophthalmic vein → sinus convergence roop (cross-talk). The second route is via a possible neural circuit traveling through lamina cribrosa (optic disc) → optic nerve bundle sheath in retrobulbar space → optic chiasm (cross-talk) → retrograde back to the opposite fellow eye. These two local short-cut routes do not go through systemic blood stream, which avoids significant dilution of drug concentration. The third route is a conventional path through systemic blood circulation (via the heart), the concentration of viral vectors or molecules will be significantly diluted (~4.5L of blood in adult) upon circulating back to the contralateral eye. For high dose local gene delivery, as we see in Spark's LCA2 trials (subretina: AAV2-hRPE65v2: 1.5×10^{11}), and Phase 1/2 trials of

Leber’s Hereditary Optic Neuropathy (LHON) by GenSight Biologics (intravitreal: rAAV-ND4: 1.0×10^{11}), these patients have achieved significant improvement of visual acuity and better visual sensitivity in non-treated fellow eyes. Nevertheless, care should be taken on patient safety. From efficacy point of view, dosing principles guide us to seek sweet spot and fine tune an optimal dose, therefore the more does not necessarily mean the better.

Looking for the future, retina gene delivery will have to move from subretinal local rescue towards intravitreal or suprachoroidal pan-retina target, as such early intervention will become a reality, that’s the ultimate goal of gene replacement or neural protection via genetic augmentation. Intravitreal or suprachoroidal delivery also enables for broad disease targets, such as genetic based drug delivery, and a simple procedure at office visit is a surplus. Unlike small molecule or antibody drug, delivering a genetic payload into neurons especially photoreceptor and RPE has been approved to be much more challenging because of significant biophysical barriers rendered by inner limiting membrane and neural sensory retina layers, which are not a problem for antibody drug penetrating to the subretina space (e.g. Eylea and Lucentis). The technical challenge of gene delivery is driving the viral vector platform innovation towards higher potency and specificity. At upstream genetic construction, a good selection of promoter and viral serotype to overcome immunogenicity and off-target as well as problems related to manufacture scale-up become the bottleneck hurdles. Of note, the intravitreal and suprachoroidal space are not immuno-privileged sites. Compared to AAV2 that has well established and clinically validated human safety profile, lentiviral vector offers appealing advantage of carrying large gene payload with greater potency but bears higher risks associated with host immunoresponses and possible oncogenicity [5]. Other AAV serotypes (AAV5, AAV8) are being tested in clinical trials with promises. To neutralize the circulating antibody to AAV may help encompass patients who are previously excluded from the trials. At downstream clinical development, to identify the rate limits of gene transfer and the prognostic factors in a given pathological condition is a “must”. At the moment, the technology can only help patient with IRD to gain mobility and some levels of independence because the target population is at late or advanced disease with low vision or legally blind. Hopefully one day soon we can leap off the ground to help patients to gain better independence, or even have a driving vision, eventually can eradicate the blindness caused by a broad visual devastating IRD such as Stargardt macular dystrophy and LHON.

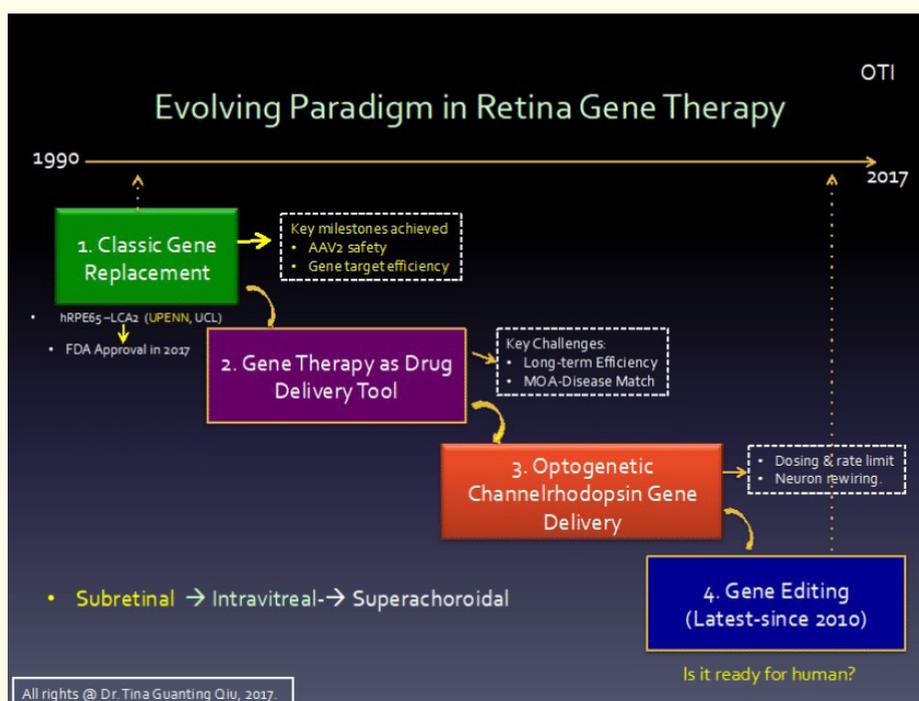


Figure 1: Evolving Paradigm of Retina Gene Therapy. Presented at Astellas Pharma special lecture, June 2017, Tokyo Japan.

Acknowledgement

Special thanks to Astellas Pharma and Sanofi Aventis for the opportunities to work on leading-edge retina gene therapy projects, which propels me to quest for these important issues discussed in the article.

Bibliography

1. FDA Brief Document of Advisory Committee Meeting Review on BLA125610 Virotigene Neparvovec, Spark Therapeutics Inc. (2017).
2. Edwards TL., *et al.* "Visual Acuity after Retinal Gene Therapy for Choroideremia". *New England Journal of Medicine* 374.20 (2016): 1996-1998.
3. JWB Bainbridge., *et al.* "Effect of Gene Therapy on Visual Function in Leber's Congenital Amaurosis". *New England Journal of Medicine* 358.21 (2008): 2231-2239.
4. Hanhart J., *et al.* "Fellow eye effect of unilateral intravitreal bevacizumab injection in eyes with diabetic macular edema". *Eye (London)* 28.6 (2014): 646-653.
5. Keshet Ronen., *et al.* "Distribution of Lentiviral Vector Integration Sites in mice Following Therapeutic Gene Transfer to Treat-thalassemia". *Molecular Therapy* 19.7 (2011): 1273-1286.

Volume 9 Issue 2 February 2018

©All rights reserved by Tina Guanting Qiu.