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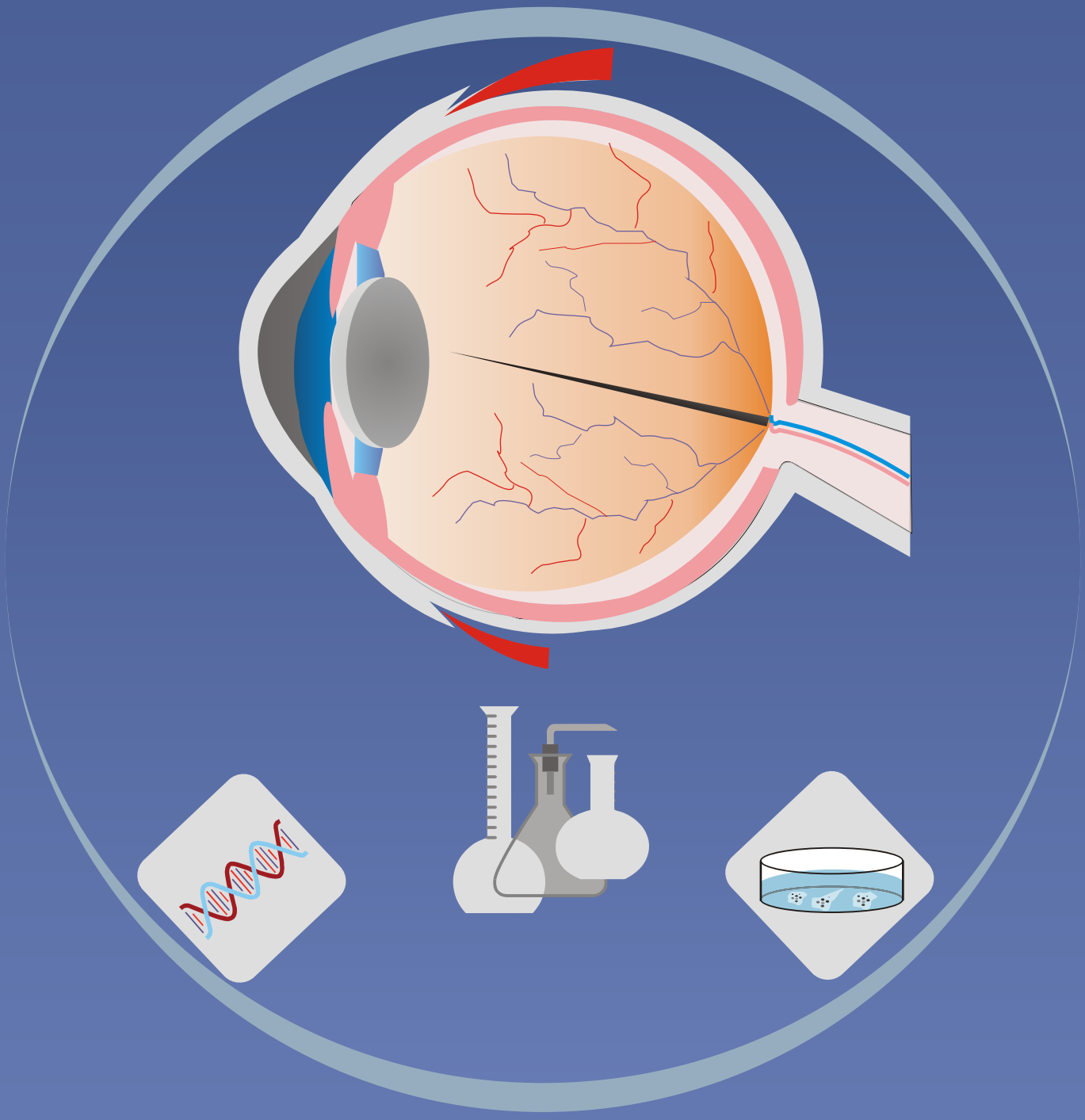
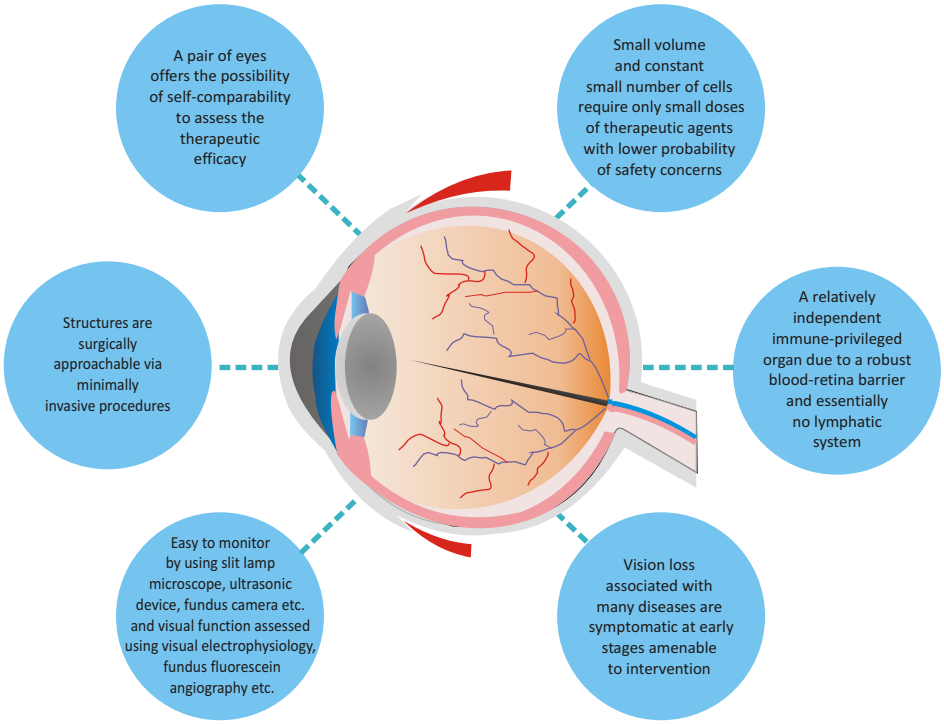
Gene & Stem Cell Therapy in Ophthalmology



Scientific progress in the fields of cellular and molecular biotechnology has led to the development of novel technologies in the form of gene therapy, somatic cell therapy, and tissue engineering, which are referred to as “Advanced Therapy Medicinal Products” by European regulators. The approval of Glybera (2012) and Holoclar (2015) in the EU is a major milestone in the evolution of the field of gene and stem cell therapy. The eye is an attractive organ for gene and stem cell therapy and sight-restoring therapy for the visually impaired and blind is a major unmet medical need. Emerging data holds out the promise of restoring sight, and efforts are ongoing to translate the potential of ocular gene and cell therapy from 'bench to bedside' in the near future.

Unique structural and functional features of eye make it an attractive target organ for gene and cell therapy



Significant progress has been made in the development of ocular gene and cell therapy for retinal degenerative and corneal disorders

The role of gene and cell therapy is currently being explored in a variety of retinal degenerative disorders. These include age-related macular degeneration (AMD) and the inherited retinal degenerations (for example, retinitis pigmentosa, Leber congenital amaurosis, choroideremia, Usher syndrome and Stargardt disease). While AMD is the leading cause of blindness in the developed world, inherited retinal degenerations are rare genetic diseases with no satisfactory treatment options. Over 200 genes responsible for inherited retinopathies have been identified over the past 10 years. Retinal disorders are characterized by a high level of genetic heterogeneity, illustrating the challenges and opportunities associated with gene therapy in these disorders. Stem cell therapy also has the potential to treat scarred and degenerative corneas. The first and only ocular stem cell therapy, Holoclar, has been approved in EU for the patients with moderate-to-severe limbal stem cell deficiency due to ocular burns.

Table 1: Status of select industry-sponsored clinical studies involving gene or cell therapy for ophthalmological indications

Indication		Asset	Type	Phase	Company
Moderate to severe limbal stem cell deficiency		Holoclar	Stem cell therapy	Approved in EU	Chiesi Farmaceutici S.p.A.
Leber Congenital Amaurosis type 2		rAAV2-CB-hRPE65	Gene therapy	Ph - I/II NCT00749957	Applied Genetic Technologies Corp
		SPK-RPE65	Gene therapy	Ph - III NCT00999609	Spark Therapeutics
Choroideremia		SPK-CHM	Gene therapy	Ph - I/II NCT02341807	Spark Therapeutics
		rAAV2.REP1	Gene therapy	Ph - I/II NCT01461213	NightstaRx
X-linked Retinoschisis		AAV	Gene therapy	Ph – I/II NCT02416622	Applied Genetic Technologies Corp /Biogen
Leber Hereditary Optic Neuropathy		GS010 / AAV2/2-ND4	Gene therapy	Ph - I/II NCT02064569	Gensight Biologics
Stargardt Disease		StarGen (SAR 422459)	Gene therapy	Ph –I/IIa NCT01367444	Sanofi
		MA09-hRPE	Stem cell therapy	Ph – I/II NCT01469832	Ocata Therapeutics
Usher syndrome	Retinitis Pigmentosa associated Type Ib	UshStat (Myosin VIIA gene therapy)	Gene therapy	Ph –I/II NCT02065011	Sanofi
	Type II/ III	NT- 501	Encapsulated Cell Therapy	Ph – II NCT01530659	Neurotech Pharmaceuticals
Retinitis Pigmentosa		NT-501	Encapsulated Cell Therapy	Ph – II NCT01530659	Neurotech Pharmaceuticals
		hRPC	Stem cell therapy	Ph –I/II NCT02320812	jCyte
		hRPC	Stem cell therapy	Ph I/II NCT02464436	ReNeuron Limited
Dry Age-related macular degeneration (AMD)		HuCNS-SC	Stem cell therapy	Ph - II NCT02467634	StemCells, Inc.
		MA09-hRPE	Stem cell therapy	Ph –I/IIa NCT01674829	Ocata Therapeutics
		OpRegen	Stem cell therapy	Ph – I/II NCT02286089	Cell Cure Neurosciences Ltd.
Wet AMD		AVA-101 (rAAV.sFlt-1)	Gene therapy	Ph - II NCT01494805	Avalanche Biotechnologies
		AAV2-sFLT01	Gene Therapy	Ph – 1 NCT 01024998	Genzyme/Sanofi
		Retinostat	Gene therapy	Ph - I NCT01678872	Oxford Biomedica
		PF-05206388	Stem cell therapy	Ph - I NCT01691261	Pfizer

Among the ocular gene therapies in development, SPK-RPE65, for Leber's congenital amaurosis type 2, is the most advanced, with statistically and clinically significant results reported recently on various end-points in the Phase III study. It has received orphan designation in the US and the European Union, and breakthrough therapy designation in the US. In early phase clinical studies, SPK-RPE65 was shown to be safe and provided a clinically meaningful benefit. The enrolled children gained the ability to walk and play and could carry out classroom activities without the need of visual aids. Recent reports suggest that this gene therapy may restore visual pathways in the brain.

In diseases such as Stargardt macular dystrophy, both gene therapy and stem cell therapy approaches are being explored. While theoretically gene therapy is a more focused approach aimed at replacing the defective ABCA4-gene, stem cell therapy in this case involves sub-retinal transplantation of human embryonic stem cells that have terminally differentiated into retinal pigment epithelial (RPE) cells. These cells have the capacity to support photoreceptor survival and preserve visual function. It remains to be seen how the two approaches would compare in terms of long-term efficacy and safety.

Will gene or cell therapy be curative?

The benefits of gene or cell therapy – curative or a mere long-acting substitute to the conventional pharmacotherapy – would depend on the mechanism of action and the underlying disease biology. In the case of inherited monogenic recessive disorders, gene replacement therapy may be potentially curative by replacing the underlying defective gene, provided persistent lifelong gene

expression can be ensured. However, data on lifelong effectiveness would be required to substantiate any such claims. On the other hand, in multi-factorial diseases, gene addition or cell therapy with genetically modified cells may positively modulate one of the underlying disease pathways and provide sustained therapeutic effects.

Two recent reports of the long-term follow-up of patients with LCA treated with rAAV2-RPE65 in Phase I/II clinical trials illustrate some challenges associated with achieving a cure. Both studies reported initial improvement in the treated eye, followed by a decline in effect over the longer term. Potential strategies to overcome this challenge have been proposed. These include development of more efficient vector delivery systems, ability to guide treatment to the areas with enough functional photoreceptors, and administration of additional rounds of gene therapy.

Visual acuity is the most relevant clinical endpoint for ophthalmology studies; other primary efficacy endpoints may be pursued

Most ophthalmology studies rely on functional or subjective endpoints as few objective end points are available. For example the regulatory approval studies of Lucentis for different indications such as wet AMD and macular edema following retinal vein occlusion (RVO), included visual acuity outcomes as the primary endpoint. Visual acuity and visual field tests are subjective but most relevant from a patient's perspective. Endpoints to demonstrate the effect of intervention on underlying pathophysiology and other symptomatology are also included. Surrogate endpoints that correlate with vision may be valuable if direct assessment of clinical benefit is not feasible. For Holoclar, the primary endpoint was the presence of a stable corneal epithelium without significant recurrence of neovascularisation. Visual acuity was a secondary endpoint in the clinical study – 49% patients showed improvement of at least one full line on a Snellen chart.

Patient reported outcomes (PROs) such as the 25-item National Eye Institute Visual Function Questionnaire (NEI-VFQ 25), are now becoming increasingly important. These are being used in AMD and RVO studies, as a supplement to clinical outcome measures to provide a more comprehensive view of the full impact of the disease and treatment.

Economic evaluation/modeling would help inform reimbursement decisions for these costly/novel interventions

Blinding eye diseases result in an increase in cost for both eye-related and non-eye-related medical care. The total economic burden of eye disorders and vision loss was reported to be $139 billion (2013). If monetary value for DALYs lost is also included ($14 billion) this increases to a total of $153 billion. Vision loss is also reported to be associated with increased risk of injury and depression. An improvement in visual acuity would reduce cost of medical and home care, proportionate to the magnitude of improvement. This may justify the high price of interventions designed to improve visual function. One such example is the Argus II Retinal Prosthesis System, an implant device to treat patients aged 25 years and older, with bare or no light perception vision caused by advanced retinitis pigmentosa. The device has been shown to help patients identify the location or movement of objects and people and recognize large letters, words, or sentences. With such clinical benefit, it is considered cost-effective at $145,000 and is being reimbursed both in US and EU.

Significant considerations and challenges exist for clinical development, regulatory approval, and commercialization of gene and cell therapy products

Some unique characteristics of cell and gene therapies influence clinical trial designs.

- Products may persist in humans for an extended period of time after administration
- Effect of the products may evolve over time
- Delivery may require surgery or other invasive procedures

The FDA has issued guidelines for the design and conduct of early-phase clinical trials of cell and gene therapy products. This guidance covers many relevant areas of clinical trial design, including early-phase trial objectives, choice of study population, control group and blinding, and dose and regimen selection.

Unlike conventional therapies, the approval of Holoclar in the EU was based on demonstration of efficacy in a multi-center, case-series, non-controlled, retrospective cohort study in 106 patients with moderate-to-severe limbal stem cell deficiency (LSCD). In the case of Glybera, the

approval was based on three open-label non-comparative clinical studies in 27 lipoprotein lipase deficiency (LPLD) patients. The small study population is justified in view of a very low prevalence, 3.361 per 100,000 for LSCD and 0.2 per 100,000 for LPLD.

However, these products have currently been authorized under a 'conditional approval' scheme and EMEA is expected to review the emerging data at least every year. Further, none of these products are yet approved in the US and the FDA has demanded additional clinical studies for Glybera.

Table 2: Prevalence of some inherited diseases causing blindness

Disease	Prevalence	Comment
Leber congenital amaurosis	1 in 40,000*	Eighteen different types based on different gene mutations. The most frequent is mutation in the GUCY2D gene (accounting for 21.2% cases), followed by CRB1 (10%), and RPE65 (6.1%)
Retinitis pigmentosa	1 in 3,750	Caused by mutations in more than 60 genes. Mutations in the *RHO* gene are the most common cause of autosomal dominant type (20-30% cases). Mutations in USH2A gene cause 10-15% of all cases of autosomal recessive type. Mutations in the *RPGR* and *RP2* genes account for most cases of X-linked type.
Leber's hereditary optic neuropathy (LHON)	1 in 23,000	Nearly 45 mutations have been linked to LHON. The most common is the 11778 mutation (50% of all cases); ~45% cases are due to 14484 or 3460
Choroideremia	1 in 67,000	Caused by mutations in the *CHM* gene

*Birth prevalence

The limited patient pool is a challenge for patient accrual in these clinical studies. Also, due to the potential curative or long-term benefits, the trial could deplete the number of the treatable population before the product gets commercialized. The slow and variably progressive nature of some of these diseases such as retinitis pigmentosa, makes it difficult to exactly predict the vision at a specific time in the future. This necessitates long-term studies on a larger patient population to demonstrate clinically meaningful benefits.

The approval of both Glybera and Holoclar has been complicated by complex and overlapping regulatory oversight. For Glybera, the marketing authorization application was first submitted in December 2009 and approval was granted in November 2012, after several rounds of assessments. For Holoclar, while the first two patients were successfully treated in 1997, orphan drug designation was granted only in 2008, and the approval was finally granted in 2015.

In view of the high price tag ($1-1.5 million) and the absence of life-long data, upfront reimbursement at the time of treatment is another significant challenge. Novel payment options, including pay-for-performance models that would distribute cost over an extended period based on effectiveness, may be considered.

Commercial manufacturing of gene and cell based therapy requires substantial investment in expensive equipment, highly skilled staff, and processes. Ensuring GMP compliance and economic feasibility for 'orphan drugs' is a bigger challenge compared with conventional pharmaceutical products due to the scarcity of the required resources.

Delivering gene and cell therapy products to patients requires capacity building in terms of establishing centers of excellence with highly skilled manpower and appropriate infrastructure for identification, evaluation, and ongoing monitoring of patients.

Conclusions and way forward

The eye, with its unique characteristics, is particularly suited for gene or cell therapy. The field of ocular gene and cell therapy is experiencing incredible momentum, driven by encouraging results in some early-stage clinical trials. However, there is a long way to go before these products can be considered truly safe and effective for treating intractable and disabling diseases of the eye. With the rapidly changing regulatory and competitive landscape, an integrated clinical, regulatory, and commercial strategy needs to be developed to maximize the return on investment in these areas.

About SmartAnalyst

SmartAnalyst helps bio-pharma companies drive pipeline and portfolio value by providing strategic consulting and analytical support for key decisions at the Disease, Asset, and Portfolio levels. Contact us to discuss how we can assist you in your gene and cell therapy product portfolio decisions.

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