FROM THE ANALYST'S COUCH

Gene therapies in ophthalmic disease

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Inherited retinal dystrophies (IRDs) encompass a group of rare disorders associated with genetic defects that cause progressive retinal degeneration. Patients have severe, bilateral and irreversible vision loss beginning in early to mid-life. There are more than 200 gene defects associated with the most common IRDs. The first FDA-approved gene therapy, voretigene neparvovec (Luxturna; Spark Therapeutics), was approved for IRDs caused by biallelic mutations in *RPE65* in adult or paediatric patients. The therapy was approved by the European Medicines Agency (EMA) in November 2018. These landmark decisions could further open the doors to gene therapies for ophthalmic diseases.

IRDs are ideal candidates for gene therapy because the responsible mutations have often been identified and, to some extent, the eye is an immune-privileged space. Clinical trials have shown that there is no substantial immune reactivity or systemic adverse events associated with treatment with adeno-associated virus (AAV) and lentivirus vectors, which are used to deliver the desired gene.

The most common IRDs are retinitis pigmentosa, choroideremia, Leber hereditary optic neuropathy (LHON), Leber's congenital amaurosis (LCA), Stargardt disease, achromatopsia and X-linked retinoschisis (XLRS); most gene therapies in development focus on these conditions. Therapies are also in development for retinal vascular diseases and age-related macular degeneration (AMD), although these conditions are not associated with a single genetic defect. In these indications, cells are genetically modified to produce proteins that block pathogenic pathways. Gene therapies for IRDs step into the larger market for ophthalmology products (BOX 1).

Luxturna is administered to patients with viable retinal cells via subretinal injection and hence patients with more advanced forms of the disease will not be eligible for treatment. Although safety and efficacy have been assessed in only 41 patients, Spark Therapeutics will be conducting a post-marketing study to confirm long-term safety. Known side effects are mainly associated with the injection procedure itself and include eye inflammation, redness and pain.

Pipeline analysis

The mode of delivery for ophthalmic gene therapies depends on the location of the target cells. In the majority of IRDs, the defective genes affect the outer retinal layers, retinal pigment epithelium (RPE) and underlying choriocapillaris. In these cases, the viral vector is delivered into the subretinal space. In the case of LHON, retinal ganglion cells are the target, so the vector is injected into the vitreous cavity for better penetration of the inner retinal layers. Also, because of concerns about the weakness of the retina

Box 1 | Ophthalmology market analysis

The total ophthalmology market generated sales of US$27.9 billion in 2017, accounting for 2.8% of the overall pharmaceutical market (see figure). The market has a compound annual growth rate (CAGR) of 6.17% over the past 5 years. The ophthalmology market is dominated by ocular angiogenesis-modifying compounds, which generated worldwide sales of $9.8 billion in the past 12 months (2017 fiscal year (FY), accounting for 35% of the total ophthalmology market).

Angiogenesis-targeted drugs have a CAGR of 11.44% (2013–2017 FY). Ranibizumab (Lucentis; Genentech) and aflibercept (Eylea; Regeneron) — top-selling angiogenesis-modifying compounds — generated sales of $3.5 billion and $6.2 billion, with 12-month growth rates of 1.3% and 15.5%, respectively. The annual sales of ranibizumab have been declining since 2015, most likely owing to the off-label use of bevacizumab (Avastin; Genentech) in wet AMD and the launch of aflibercept; both bevacizumab and ranibizumab inhibit vascular endothelial growth factor, but bevacizumab is approved for cancer therapies, not AMD. Aflibercept's growth trajectory is likely to continue, fuelled by broad approved indications in addition to potential approvals in other indications, including diabetic retinopathy without diabetic macular oedema. Additionally, aflibercept has more convenient dosing and is cheaper than ranibizumab. Ranibizumab is expected to lose exclusivity in 2020; biosimilars will enter the market thereafter and, if successful, will disrupt the market.

Miotics (which stimulate the parasympathetic nervous system and cause pupil dilation) and anti-glaucoma preparations generated sales of $6.0 billion in 2017, accounting for 22% of the ophthalmology market, followed by products for dry eye, with sales of $4.5 billion.

Spark Therapeutics' gene therapy, Luxturna, generated sales of $6.7 million in the first 6 months of 2018. Spark launched Luxturna in the US in the first quarter of 2018, at a price of $450,000 per eye or $850,000 for both eyes. Incremental cost-effectiveness ratio analysis has suggested this price is 50–75% higher than is considered cost effective, assuming that the benefit lasts for 10–20 years. However, Spark has rolled out payment programmes to help spread the cost. Analysts' expected peak sales for Luxturna vary widely: from $350 million to $750 million by 2022.

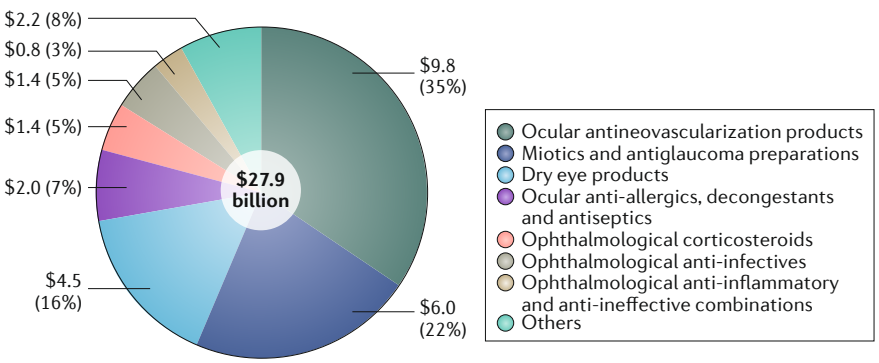

Table 1 | **Selected gene therapies in development for ophthalmic diseases**

Indication	Vector	Sponsor	Highest phase
Achromatopsia	rAAV2tYF-PR1.7-hCNGB3	AGTC	II
Achromatopsia	AAV-CNGB3	MeiraGTx	II
Achromatopsia	AAV-CNGA3	MeiraGTx	II
Achromatopsia	AAV2tYF-CNGA3	AGTC	I/II
Choroideremia	NSR-REP1	Nightstar Therapeutics	III
Choroideremia	AAV2-hCHM (SPK-7001)	Spark Therapeutics	II
Leber congenital amaurosis	rAAV2-CB-hRPE65	AGTC	II
Leber congenital amaurosis	AAV-RPE65	MeiraGTx	II
LHON	AAV2-ND4	GenSight Biologics	I/II
Neovascular AMD	AAVCAGsCD59 (HMR-59)	Hemera Biosciences	I
Neovascular AMD	RetinoStat / OXB-201 (LV)	Oxford BioMedica	I
Neovascular AMD	AAV8-anti-VEGF (RGX-314)	Regenxbio Inc.	I
Neovascular AMD	AAV2-sFLT01	Genzyme (Sanofi)	I
Retinitis pigmentosa	AAV-ChR2 (RST-001)	RetroSense Therapeutics/Allergan	II
Retinitis pigmentosa	AAV2/5-hPDE6B	Horama	II
Retinitis pigmentosa	HORA-RPE65	Horama	II
Retinitis pigmentosa	GS030-DP	GenSight Biologics	I/II
Retinitis pigmentosa	AAV8-hRLBP1	Novartis	I/II
Retinitis pigmentosa	AAV2-hMERTK	Fowzan Alkuraya	I
Stargardt disease	SAR422459 (LV)	Oxford BioMedica/Sanofi	II
Usher syndrome type 1B	UshStat (LV)	Oxford BioMedica/Sanofi	II
XLRP	rAAV2tYF-GRK1-RPGR	AGTC	II
XLRP	AAV2-RPGR	MeiraGTx	II
XLRP	AAV-RPGR (NSR-RPGR)	NightstaRx Limited	II
X-linked retinoschisis	rAAV2tYF-CB-hRS1	AGTC	II

AAV, adeno-associated virus; AGTC, Applied Genetic Technologies Corporation; AMD, age-related macular degeneration; LHON, Leber hereditary optic neuropathy; LV, lentivirus; XLRP, X-linked retinitis pigmentosa.

in XLRS, an intravitreal approach has been preferred for this disorder.

There are 25 gene therapies currently in phase I, II or III development (TABLE 1). These cover a range of ophthalmic diseases, including IRDs such as retinitis pigmentosa and LCA as well as AMD and uveal melanoma. Applied Genetic Technologies Corporation (AGTC) and MeiraGTx lead the drive in ophthalmic gene therapies, with five and four assets in development, respectively.

The phase II space is the busiest, with nineteen therapies at this stage, including five in development for retinitis pigmentosa, four for achromatopsia and two for LCA.

Most of the therapies in development aim to restore expression of the mutated gene (namely *CHM*, which encodes RAB escort protein 1 (REP1), *CNGA, CNGB, RPE65, RS1* or *RPGR*). Notable exceptions include therapies for AMD, in which the gene therapy encodes a therapeutic molecule to inhibit angiogenesis or inhibit cell death, and RST-001, which delivers channelrhodopsin 2, a gene that confers photosensitivity.

NightStar's AAV2-REP1 for choroideremia is the closest to potential approval, and is the only therapy in phase III. NSR-REP1 (AAV2-REP1) is an AAV2 vector containing recombinant human complementary DNA to produce REP1 in the eye. The phase III study is anticipated to complete global recruitment of 140 patients in Q1 of 2020.

Current challenges in gene therapy

Although the first gene therapies (Glybera, Imlygic and Luxturna) have successfully overcome barriers to clinical development, substantial challenges remain for production, clinical study design, long-term safety studies and commercialization of future gene therapies. Before they can receive investigational new drug (IND) status from the FDA, gene therapies require well-controlled manufacturing processes and validated analytic assays for all critical quality attributes, because of the inherent complexity and potential for variability between production cycles. Additional biodistribution studies are also required during early preclinical development to ensure that the transgene is expressed as expected and is not delivered to non-target tissues. To help overcome these early development challenges, the FDA encourages gene therapy developers to communicate with the agency early on, via an initial targeted engagement for regulatory advice on CBER products (INTERACT) meeting prior to the pre-IND meeting.

Careful planning for clinical development is also required to avoid delays or additional study requirements. Approval for gene therapies is often accelerated and based on the results of phase I/II and phase IIb studies; therefore, careful selection of study end points, patient inclusion and exclusion criteria, and clinical site selection are critical. For viral vector-based gene therapies, the need to screen for anti-vector antibodies can impose a substantial restriction on the available patient population, which should be incorporated into cost and timeline projections. Increasingly, both the FDA and payers are seeking patient experience data that can be captured during clinical development, either as a primary end point (as for Luxturna), or as supplementary evidence. Planning to capture patient experience data on an ongoing basis, along with required long-term safety follow-up, offers efficiencies and synergies with commercial strategy.

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https://doi.org/10.1038/d41573-018-00016-1

Competing interests
The authors declare no competing interests.

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