What does the future hold for ophthalmic drug delivery?

Drug delivery to the retina needs a revolution.

Analysis of global ophthalmic drug pipelines suggests that the trend in 2035 will be towards strong growth in cell and gene therapies targeting high-prevalence diseases of the retina. However, cell or gene therapies can only access the retina if they are delivered directly into it, and existing sub-retinal delivery techniques cannot scale to more than a few percent of the number of procedures which will be required. A radical re-think of sub-retinal drug delivery is needed.

This level of procedural simplification has happened before in many areas of medicine and surgery, and - to our knowledge - always been enabled by a complete rethinking of the tools.

There is time to think big and revolutionise drug delivery to the retina - but there is no spare time.

Drug delivery to the eye is changing

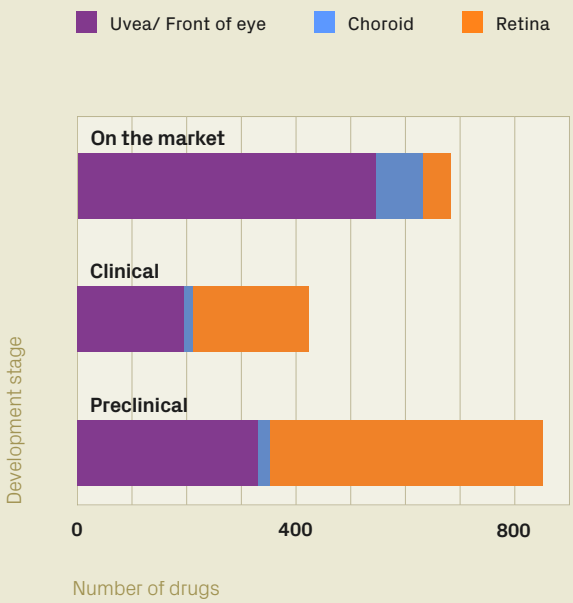
The pharmaceutical industry is always in flux - it's the mark of a healthy technology sector. Drugs for the eye are no exception - whereas 20 years ago the landscape was dominated by small molecules, the last ten or fifteen years has seen the rise of biologics and an increasing focus on diseases of the back of the eye. This has, in turn, driven a revolution in workflows to enable ever-growing numbers of intravitreal injections to be administered with an astonishing safety and efficacy profile.

Changes over the last ten years have been profound; what will drug delivery to the eye look like ten years from now?

Our analysis of public data on drugs for the eye planned for launch in the US or Europe gives an unusually clear answer to this question:

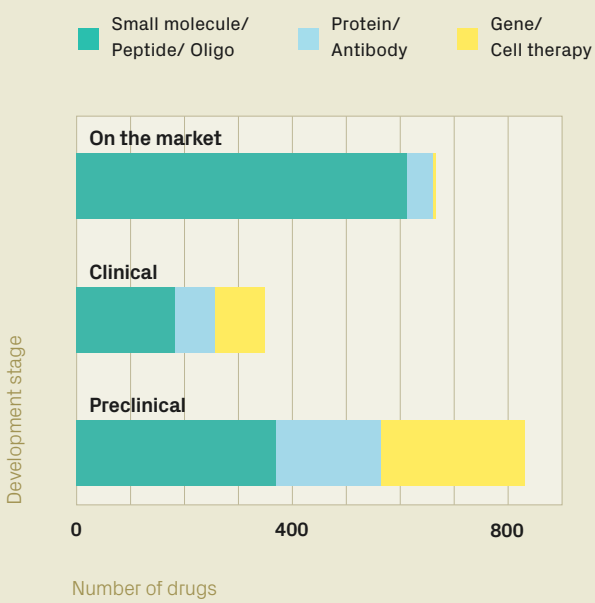
the trend in 2035 will be towards strong growth in cell and gene therapies targeting high-prevalence diseases of the retina.

Fig 1. Ophthalmic drugs by target site and development stage



Source: Global Data

Fig 2. Ophthalmic drugs by drug class and development stage



Source: Global Data

Even though many of the drugs in pipelines - especially those in preclinical stages - will not progress to become marketed therapies, drop-out in the drug discovery process is unlikely to change our basic conclusion. Looking first at the target site (figure 1), whereas only about 10% of marketed therapies target the retina, more than half of preclinical assets do. A large majority of the 500 pre-clinical assets in this analysis which target the retina will never come to market, but it is clear that drugs targeting the retina will be a much larger proportion of new than current drugs.

Considering class of therapy (figure 2), the story is very similar: by number, present therapies are mostly small molecules (though biologics are more significant by value, and arguably by impact); in the preclinical pipeline, small molecules are a minority, with cell therapy and gene therapy approaching a third - amounting to more than 250 assets.

The trend is clear, and robust. So when these pipeline assets come to fruition, what might be implications for delivery be?

Is delivery ready for these new drugs?

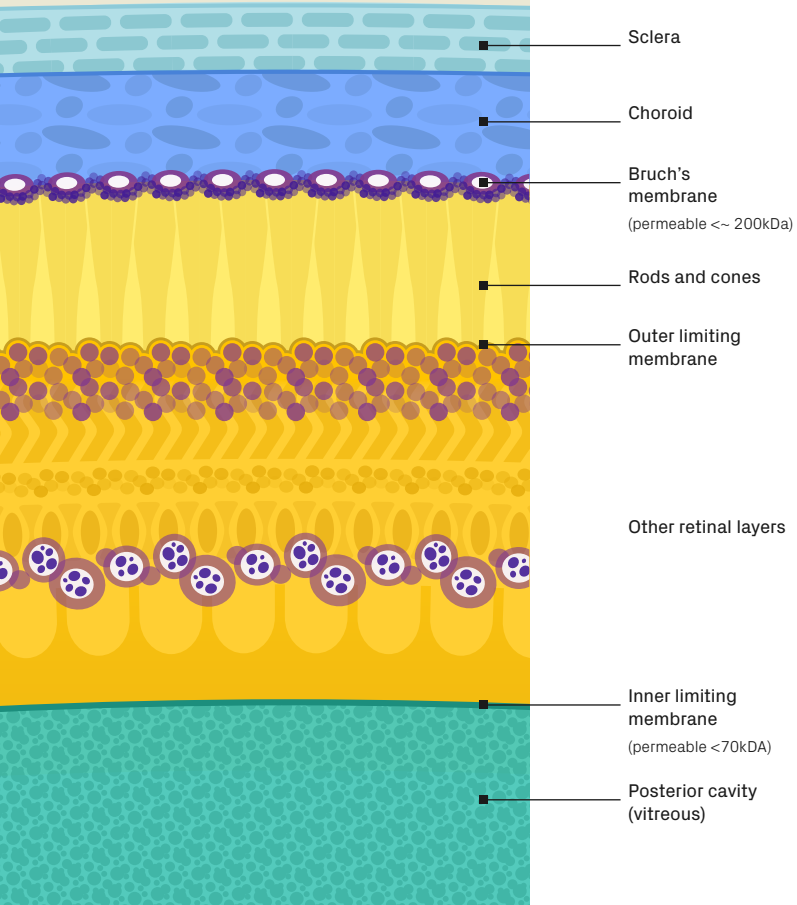
At present, drug delivery to the eye is very strongly dominated by eye drops and intravitreal liquid injections. Eye drops are mostly self-administered and provide an effective (though weakly-targeted) method to deliver small molecules to the front of the eye. Intravitreal therapies are administered by healthcare professionals, mostly in non-surgical settings, delivering both small molecules and biologics, mostly to the back of the eye; it has been estimated that around 15 million intravitreal therapy (IVT) injections were performed in the US in 2024.

Can either of these two heavy-weight techniques serve the upcoming need to deliver cell and gene therapies to the retina to treat high-prevalence diseases such as AMD, DME, and GA?

The answer to this is primarily driven by anatomy: what structures exist in the eye between the retina and the location where the delivery technique deposits the formulation which might limit the spread of cells or gene vectors?

There are essentially two ways into the retina: through the front from the vitreous, and through the back from the choroid (figure 3). Both routes are regulated by selectively permeable membranes: Bruch's membrane controls entry from the choroid, allowing in only molecules under about 200kDa (more like 100kDa in older age); and the inner limiting membrane controls entry from the vitreous, restricting the ability of molecules above about 70kDa to access the retina.

Fig 3. Posterior section of the eye showing sclera, choroid, and retinal layers; layer thicknesses are not to scale.



By comparison, a gene therapy with an AAV vector is about 5MDa - therapeutic cells are, of course, far bigger. Even without considering the effects of outflows from the eye and of degradation, it is clear that - exceptional circumstances apart - if cell or gene therapies are delivered outside of the retina, they will stay outside of it.

Exceptional circumstances do occur. For example, a cell therapy may treat the retina by introducing cells into the vitreous which then manufacture a therapeutic which is small enough to pass into the retina. Or again, neither membrane is as simple as a sieve, so slightly larger molecules with appropriate chemical properties will penetrate to some extent. But the gap in size between membranes “cut-offs” and even a small gene therapy is very large: delivery outside the retina will often be insufficient.

So eye drops and IVT will not cover many of the next generation of retinal therapies - are there other existing techniques which might work?

There are existing methods for delivering therapies sub-retinally, of which the more established involves accessing the retina from the front via ports in the anterior sclera, typically post-vitrectomy. Another approach (presently still in trials) involves threading a cannula through an incision in the sclera and along the suprachoroidal space, then extending a fine needle into the retina from behind.

Both techniques have a number of limitations. The rate of complications (>50%) and serious adverse events (>1%) is relatively high compared to IVT and - as surgical procedures - they are far more time-consuming (one to two hours vs around 15 minutes) and expensive (>$10k vs around $600).

But by far the biggest limitation is availability: there are presently fewer than 20 centres in the US which are able to deliver these sub-retinal procedures, but even if the entire surgical effort of US retinal specialists were redirected to sub-retinal drug delivery, it would still only enable around 1,500,000 treatments per year. With more realistic constraints, 150,000 might be achievable.

Even if the dosing regimen for newer drugs were to reduce the number of procedures needed significantly, this is not a near-miss compared to 15 million IVT procedures per year: the capacity of the health system to deliver sub-retinal drugs is only a few percent of what is needed.

Drug delivery to the retina needs a revolution.

How must delivery devices adapt for advanced ocular therapies?

Having said retinal drug delivery needs a revolution, it's a short step to the need for radically improved delivery tools. The reason is simple: the only way to deal with the essential problem of surgical bandwidth is to reduce the complexity and invasiveness of the procedure to the point where it takes far less time, does not require the same limiting level of skill - and ideally even ceases to be considered a true surgical procedure, much as has already happened with IVT. This level of procedural simplification has - to our knowledge - always been enabled by a complete rethinking of the tools.

So, what does a radically improved delivery tool look like? A lot remains to be determined, but the following key points are probably requirements.

- **It needs to deliver directly to the retina.** This almost certainly means introducing a very fine needle (often 48G) into the retina, probably at an acute angle to the surface to avoid issues with the bevel length.
- **It must be much less invasive than the standard of care.** This probably means avoiding the need for vitrectomy and for multiple ports in the sclera. The sub-retinal via SCS approach currently in trials has gone some way towards this.
- **It must be compatible with the needs of cell and gene therapies.** Amongst other things, this means that the system (perhaps including accessories) must be closed to avoid viral contamination of the environment, and offer low-shear fluidics to avoid damage to cells.
- **It must de-skill the procedure - and ideally remove it from the OR.** This is a high bar - and one which varies by territory - but the essence is achieving very low infection risk, very low complication rate, and a procedure which is both quick and simple.

These requirements are a significant challenge - so is there any reason to think that they might be achievable?

For now, a good way to consider this is to look at the development of procedures in other areas of surgery - and aortic valve replacement is a good comparison, involving detailed structure, difficult access, and high criticality. The evolution of early open procedures - taking five hours with full sternotomy and cardiopulmonary bypass - into current transcatheter procedures taking as little as 45 minutes and an incision of less than a centimetre gives some insight into what might be achieved in retinal delivery.

The example of aortic valve replacement suggests the need to think hard about the following points.

- **Think differently about access routes.** Identifying a means of accessing the target site by a minor incision in a much less sensitive location - avoiding more traumatic direct-access - is key. The exploration of sub-retina via SCS is promising in this regard, though the challenge of choroidal haemorrhage suggests there is more still to achieve.
- **Effective imaging for location.** Indirect access always makes visualisation harder, so a combination of imaging techniques is needed both to guide the clinician to the site and to enable a fine procedure to be performed having reached it. Ophthalmology is quite well-equipped with imaging approaches, which is a great advantage.
- **Robust stabilisation when the tool reaches the procedure site.** "Anchoring" the tools to a solid reference point close to the procedure site is vital for enabling precision and avoiding "jitter". A good mounting point is solidly connected with the target.

Aortic valve replacement is not a unique example of profound developments in surgery - the challenges of retinal drug delivery are substantial, but there's every reason to think they can be met.

Is there time to bridge the gap?

Pharma pipelines look around ten years into the future - how does that compare to the time that a revolutionary procedure and device will take to come to fruition?

Our own extensive data on product development show that developing a drug delivery device from a clear vision and a clean sheet to verification testing takes four to five years, with scaling and regulatory work fitting around that timescale. But in this case, where transforming the procedure and creating the product are so interconnected, the device vision is not - and cannot yet be - clear.

In situations like this, it almost never makes sense to begin developing a commercial product straight away - it will either be too flexible to be economical or easy-to-use, or be built on assumptions which cannot possibly be evidenced at this stage.

Instead, the better approach is usually to create tools to learn with: focused devices which test approaches and assumptions about core procedure and product direction - clinician needs and preferences, testing on animal eyes ex-vivo, in-vivo animal testing, cadaver work, and perhaps first-in-human trials. These tools are designed for ease of iteration and flexibility, not cost and manufacturability; for function and handling, not appearance.

They are not an “early prototype” of an eventual product; they are a key means by which the product is defined. How long this takes is very context-dependent, but it is usually several years.

Comparing these activities to typical pipeline timescales, there is time to think big and revolutionise drug delivery to the retina - but there is little time to spare.

About TTP's ocular drug delivery team

Reliable delivery for complex anatomy and real-world use

Delivering drugs to the eye demands accuracy at a microscopic scale, alongside a deep understanding of how devices are used in practice. At TTP, we design ocular drug delivery systems that balance anatomical precision, usability and manufacturability - helping advanced therapies reach patients safely and effectively.

Our teams bring together expertise in engineering, fluidics, optics, human-centred design and ophthalmic procedures to tackle the challenges of both front- and back-of-eye delivery.

From improving adherence in topical treatments to enabling confident surgical delivery for posterior segment therapies, we help clients make informed decisions early and progress with confidence.

With experience spanning topical, intravitreal, suprachoroidal, and subretinal delivery - and encompassing gene therapies, sustained-release implants, and novel injection systems - we support development from early concept through to scale-up and manufacture.

The result is delivery systems designed to work reliably in high-stakes clinical environments, while meeting the practical realities of commercialisation.

Let's talk ↗

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