Expert Opinion

Sustained transscleral drug delivery

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Transscleral delivery is an emerging, high-potential method for delivering drugs to the posterior eye. If successful, it could offer non-invasiveness comparable to drops and delivery efficiency comparable to intravitreal injection. However, there are numerous challenges to be overcome before transscleral delivery will be a significant treatment option. The resistance of the sclera is extremely well understood, but the other tissues, especially the retinal pigment epithelium, clearly demand more attention and the effect of drug chemistry remains poorly understood. In this review, the major research on transscleral delivery with an emphasis on current understanding of these points and open questions for the field is summarized.

Keywords: age-related macular degeneration, drug delivery, ophthalmology, retinal pigment epithelium, sclera

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1. Introduction

Diseases of the posterior eye account for a significant majority of blindness cases in the US [1]. In glaucoma, the optic nerve head damage secondary to elevated intraocular pressure (IOP) is generally untreated, with most focus on medical or surgical intervention to reduce IOP, but for other major diseases, medical treatment of the posterior segment is an important option. Of particular note is age-related macular degeneration (AMD), which is the leading cause of blindness among persons > 70 years of age [2]. Many new drugs have been identified to treat AMD, especially the 'wet' form associated with neovascularization of the retina and choroid. These drugs, the dominant of which are pegaptanib (Macugen®, Pfizer) and ranibizumab (Lucentis®, Genentech), have had varying degrees of success, limited in a large part by the challenge of delivering drugs to the posterior segment. The situation is similar for diabetic retinopathy and the reader is referred to a recent review [3] for more details on drug treatments for both AMD and diabetic retinopathy. In short, the development of new drugs has outpaced the development of methods to deliver them, creating a major challenge to our community.

As summarized nicely by Geroski and Edelhauser [4], there are four major routes for posterior segment drug delivery: systemic, topical, intravitreal and transscleral. The systemic route has the obvious advantage of easy administration, but it is largely ineffective because of the small volume of the eye relative to the entire body and the resistance of the blood–retinal and blood–vitreous barriers. The net effect of these factors is to require a prohibitively large systemic dose to achieve any significant dosage to the retina. Targeted schemes have also been developed, in which a systemically-administered drug selectively accumulates in areas of neovascularization. Verteporfin (marketed as Visudyne® by Novartis) is a selective therapy that is triggered photodynamically. The drug is administered systemically, accumulates preferentially in the neovasculature and is then activated by a laser directed at the macula. Although systemic side effects are minimal, the vertporfin approach requires multiple treatments and can cause light sensitivity

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for a few days following therapy; it is generally used in conjunction with other therapies. Topical delivery is extremely effective for the anterior segment; however, for the anterior segment, losses to the tear film, convection of drug by the circulating aqueous humor (which flows posterior-to-anterior through the pupil, away from the target area), obstruction by the lens-iris diaphragm and the long distance to the retina combine to reduce the efficiency of topical delivery to a level only slightly above that of systemic delivery (a detailed analysis is presented in [5]).

Intravitreal injection has the enormous advantage of the drug being localized at the injection site near the target tissue. Unfortunately, any violation of the globe increases the risk of infection and patient tolerance is poor. These flaws notwithstanding, intravitreal injection remains the preferred method to treat retinal diseases and new methods for sustained intravitreal release are emerging steadily. Examples include implantable devices (e.g., Bausch and Lomb's Retisert for fluocinolone acetonide, discussed in [6], Surmodics' I-vation for triamcinolone [7] and other experimental designs [8,9]) and injectable particles [10-12]; for further information, the reader is referred to recent reviews [10,13].

Transscleral delivery is a relatively new concept that could provide localization similar to that of intravitreal injection with safety levels approaching those of systemic or topical delivery. The sclera has a large surface area and is quite thin and porous, making it an appealing potential route for delivery to the posterior eye. Many recent studies have explored transscleral delivery and this review emphasizes those studies and, in particular, what can be understood about the transscleral delivery route from them. Excellent reviews on specific topics, including pharmacokinetic modeling [14], periocular delivery (including transscleral delivery) [15] and retinal drug delivery [16] are available for the reader interested in pursuing those aspects of posterior segment delivery more deeply.

2. The transscleral delivery pathway

Figure 1 shows anatomical and schematic views of the transscleral delivery pathway. The drug undergoes clearance from the scleral surface to the blood flow through the episcleral veins and to the conjunctival lymphatic system. The choroid, with its vast network of blood vessels, presents the next barrier to the diffusing drug molecules. The choriocapillaris could potentially act as a sink to drug molecules diffusing across it, although recent studies suggest that this effect may be less pronounced than previously feared.

The tight junctions of the retinal pigment epithelium (RPE) have been shown to act as a barrier for drugs diffusing through the retina. Macromolecules injected into the bloodstream were found to escape through the walls of the choriocapillaris and penetrate the Bruch's membrane only to be stopped by the junctions of the RPE [17]. Another phenomenon that works against the drug permeating through the blood–retinal barrier is the presence of active and facilitated transport systems that are located in the RPE, which clear compounds from the vitreous with a directionality towards the plasma [18]. This counterdirectional transport of subretinal fluids, mainly water, could hinder the drug from entering the vitreous. There could also be loss of the drug via losses to the choroidal flow as the drug is cleared, or to the anterior eye by lateral diffusion of the drug across the conjunctiva and diffusion from the vitreous through the porous hyaloid membrane.

3. Devices and release systems

As reviewed well by [19], simple injection in the episcleral space is insufficient to provide effective delivery to the posterior eye. The rate of loss to the surroundings is simply too high. In effect, the delivery problem is reduced to a competition between diffusion across the various barriers (sclera, RPE, choroid, Bruch's membrane), which is desirable but slow, and convection by the conjunctival circulation, which is undesirable and fast (relative to diffusion) under normal circumstances. Therefore, successful delivery systems generally fall into two strategic categories: to minimize losses to the surroundings while maintaining steady transscleral flux of the desired drug, and to deliver drug across the sclera very rapidly so as not to allow time for losses to become significant.

Controlled release of drugs from polymers is a well established research field and its ideas and technologies are now being brought to bear on transscleral delivery. The polymer offers the advantages of preventing rapid washout by the surrounding fluids and allowing a large amount of drug to be released slowly, obviously preferable to repeated injections. As with any evolving technology, multiple approaches are under consideration; these are summarized in **Table 1**. A complementary approach to containing the drug within a protective impermeable case has recently been demonstrated to be feasible [20]. Although to the authors' knowledge it has not yet been attempted, it appears both possible and attractive to combine the two approaches by encasing a polymer-based release system, providing well-managed release over a long period of time.

Iontophoresis, in which the drug is delivered via an electrode placed on the eye, relies on two different factors to improve delivery. First, the electrode surrounds the drug solution, serving as a containment device similar to that in reference [20]. Concurrently, a voltage is generated between the electrode and the ground, driving the drug into the eye electrophoretically. The potential of transscleral iontophoresis is considerable, leading to a number of investigations (e.g., [21-25]) and new companies (e.g., Aciont, Eyegate). Iontophoresis has the obvious disadvantage of requiring electrodes and a power source, but its potential is large, especially as a bolus delivery method to replace intravitreal injection. Further information on

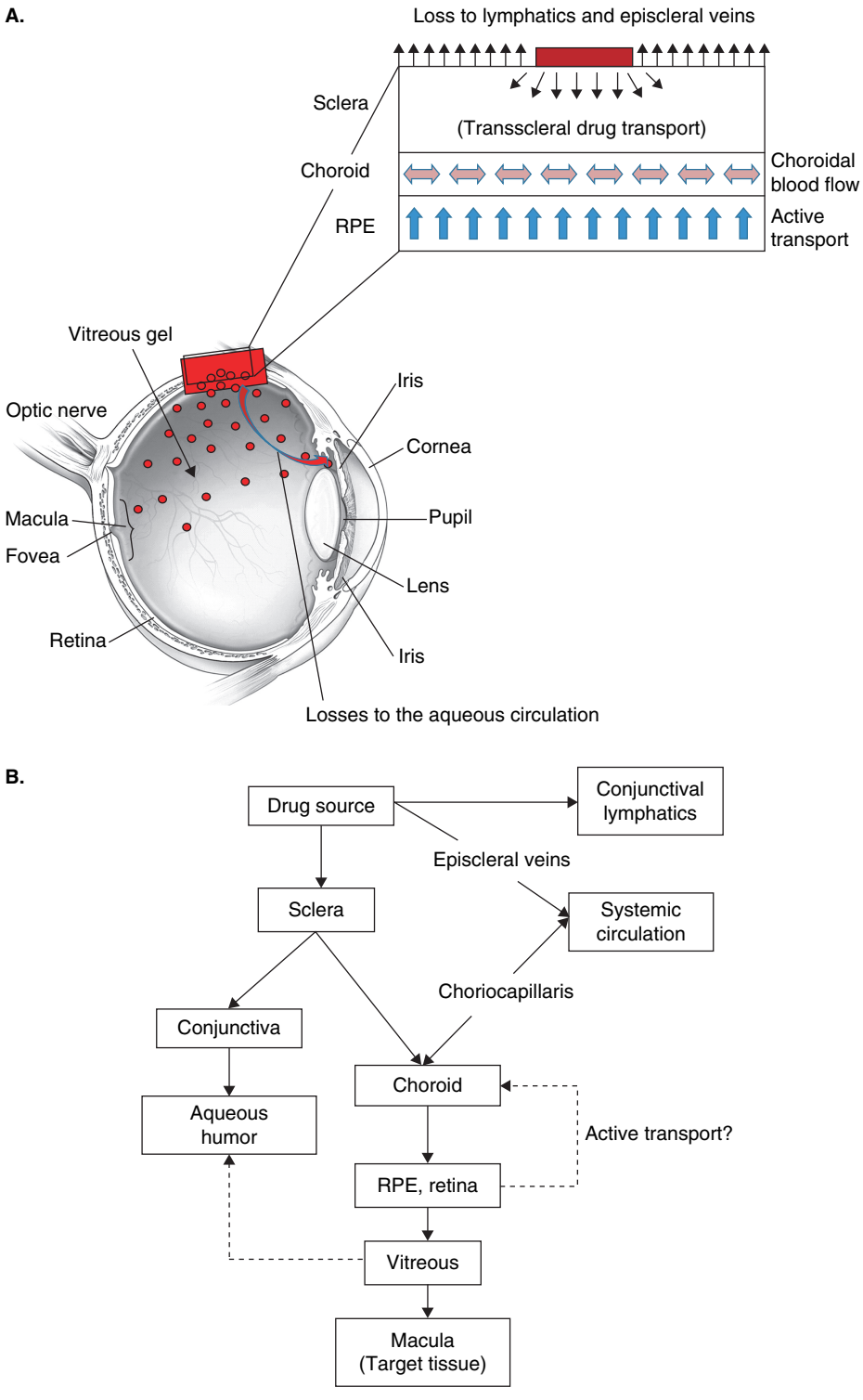

Figure 1. A. Schematic of transscleral drug delivery. The drug must cross the sclera, choroid, neuroretina and RPE, then enter the vitreous humor and diffuse to the macula. Any of the intervening tissues could provide a significant barrier, with choroidal blood flow and active transport by the RPE possible considerations. **B.** Flowchart of delivery pathways. The various paths require steps from one tissue to the next, with drug losses possible to the systemic circulation (also a possible source, as in systemic delivery), the aqueous humor (which would eventually lead to the systemic circulation) or the conjunctival lymphatics. Transport among different tissues may depend on molecular size and chemistry.

RPE: Retinal pigment epithelium.

Table 1. Transscleral controlled-release systems.

Ref.	Scaffold	Geometry	Drug	Notes
[63]	PLGA	Microspheres (15 μm)	RNA aptamer	*In vitro* study
[64]	PLA	Microspheres (3.6 μm) Nanospheres (345 nm)	Budesonide	Microparticles gave high tissue levels of drug over two weeks
[65]	PVA	Disk (1 mm)	Betamethasone	Vitreous concentration peaked at day 14 of 30-day study
[66]	PVA/EVA	Disk (1 mm)	Betamethasone	EVA coating controlled release rate
[67]	PLGA	Film (100 μm)	Etacrynic acid	Significant effect on intraocular pressure at day 3, 7, 10 of 21-day study
[68]	Collagen	Gel	Cisplatin	Most drug lost by 14-day measurement
[69,70]	Fibrin	Gel	Dexamethasone	*In vitro* feasibility studies
[71]	Fibrin	Gel	Carboplatin	Significant reduction in tumor burden versus control (fellow) eye after 22 days

EVA: Ethyl vinyl acetate; PLA: Polylactic acid; PLGA: Poly(lactic-co-glycolic) acid; PVA: Polyvinyl alcohol.

transscleral and transdermal iontophoresis is available in recent reviews [26,27].

4. *In vitro* and *ex vivo* studies

Numerous *in vitro* studies have been performed to measure transscleral flux under controlled circumstances. Although these studies have only partial clinical relevance, they do provide a direct and well controlled look at transscleral transport. The essential strategy is the same for nearly all studies, with a scleral sample being mounted between a compound-rich and a compound-poor reservoir. One or both reservoirs may be stirred and/or perfused and the state of the reservoir (and therefore of the boundary layer near the scleral sample) can depend on the quality of mixing, so caution must be taken in comparing the results of different studies, especially from different researchers.

Early work on the problem was summarized well by Prausnitz and Noonan [28] who surveyed reports of the permeability of the sclera to 21 different compounds of various chemistry and molecular weight. Prausnitz and Noonan reported that the permeability is a strong function of molecular radius, but not dependent of lipophilicity, as described by the partition coefficient of the compound between water and octanol. This important conclusion, affirmed by more recent studies of fluorescent molecules over a wide range of molecular weights [29], continues to be an accurate assessment of *in vitro* transscleral transport: molecular radius is the dominant factor in determining scleral permeability to a given species.

Subsequent work by Kao *et al.* [30] showed similar behavior for antibiotics, with the large molecules permeating more slowly. In addition, Kao observed that small amounts of vancomycin, the least soluble of the chemicals studied, appeared to precipitate, which would reduce the solution concentration below the apparent value and, thus, decrease the measured permeability. Finally, it is notable that the addition of the surfactant benzalkonium chloride had no significant effect on the transscleral diffusion of a betamethasone 21-phosphate (BP) [31], consistent with the notion that lipophilicity plays little role in transport across the isolated sclera.

The *in vitro* experiment is, of course, far removed from the physiological situation. *Ex vivo* studies provide a more accurate model, but still retain some of the ease of control and analysis that are impossible *in vivo*, allowing the exploration of complex phenomena in isolation. For example, the role of the RPE is poorly understood and, thus, has been the subject of considerable study. In the late 1980s, Tsuboi and Pederson [18,32] showed that the monkey RPE can pump water across itself indirectly via osmotic flow arising from ion transport. A recent study of RPE-choroid permeability [33] suggested that the RPE presents a significantly larger barrier to transport than the sclera does and also reported asymmetry in transport of some compounds, with inward (choroid-to-retina) transport being significantly faster than outward transport for the more lipophilic species. The greater resistance of the choroid was confirmed by another study [34], which also reported that the choroid was the major barrier to transport of small lipophilic molecules. A series of studies [35-37] led to the conclusion that although Bruch's membrane permeability decreases with age, the RPE remains the dominant resistance to transport, at least for taurine, with no significant asymmetry in transport. The importance of lipophilicity was further examined by comparing transport of (lipophilic) diazepam and (hydrophilic) mannitol across isolated sclera and sclera-choroid-retina [38]; the investigators reported that mannitol had greater permeability than diazepam across the sclera only, but that diazepam had greater permeability than mannitol across the combined sclera–choroid–retina layer. No significant asymmetry between inward and outward permeability was observed.

5. *In vivo* studies

Because of the novelty of transscleral delivery systems and the expense and complexity of *in vivo* sustained delivery experiments, such studies are relatively rare. A major challenge in the *in vivo* experiment is assessment: either a non-destructive analytical method must be used or the animal must be sacrificed, allowing only one time point (multiple time points can of course be achieved by using multiple animals, but the intersubject variability can make interpretation difficult). Fluorescein is thus a popular drug surrogate [20,39], with fluorophotometry allowing assessment of biodistribution to the different ocular tissues over time. The fluorophotometric approach is rapid, cheap and accurate, but it has the disadvantage that it can be applied only to fluorescent molecules, limiting its general applicability. Nevertheless, it is our opinion that fluorescent markers are the ideal initial *in vivo* delivery model. A similarly non-invasive, but more costly, approach is to use magnetic resonance imaging (MRI) to track biodistribution [40-42]. Like fluorophotometry, MRI requires an easily-identified target (such as gadolinium) and its cost and resolution can present challenges. The availability of three-dimensional biodistribution data, however, cannot be overlooked and, at present, MRI remains the best way to obtain such information. MRI has also been adapted to assess ion motion in transscleral iontophoresis [43]. Microdialysis, in which a continuous sampling probe is inserted into the vitreous, is more invasive than the above techniques and gives no spatial resolution (the only point measured being the tip of the probe), but it can be performed over time in a live animal and, thus, can be classified as minimally invasive. Any target molecule that can be detected in the dialysate can be targeted, which is a considerable advantage over MRI and fluorophotometry, but the lack of spatial resolution and the need to insert the probe limit the applicability of microdialysis. For further information on microdialysis in the eye, the reader is referred to a recent review [16].

An alternative to the non-invasive or minimally-invasive methods is to sacrifice the animal, dissect the eye and then analyze the separate tissues for the drug. Doing so has the obvious disadvantage that the animal must be sacrificed, increasing cost and requiring multiple animals to get a time sequence and there is the risk of diffusion among tissues during preparation (requiring rapid isolation), but it allows more detailed biochemical analysis, typically by high performance liquid chromatography [44-48] or atomic absorption spectroscopy [49,50]. Furthermore, histology can also be performed on the tissue, so some assessment of the practical impact of the treatment, not just the drug concentration, can be achieved [45,51]. Histology is particularly important when local tissue damage is a concern, as was recently reported following periocular injection of carboplatin in children with retinoblastoma [52] or when exploring a new material as a delivery platform [53].

Three *in vivo* studies provide particular insight into the mechanisms of transscleral delivery. Okabe *et al.* [31] implanted a pump into a rabbit model and measured BP levels in retina/choroid (combined) and vitreous after 1 week of treatment. The levels of BP in both retina/choroid and vitreous increased significantly when the surfactant benzalkonium chloride was added to the drug solution. This result, in conjunction with Okabe's observation that the surfactant had no effect on permeability of isolated sclera, is compelling evidence for the importance of chemistry in biodistribution of transsclerally delivered drugs even though size is the predominant factor for determining scleral permeability. The specific chemical effect is less clear from the experiment; Okabe suggested that benzalkonium chloride may have acted on tight junctions in the RPE and, thus, increased RPE permeability. Robinson *et al.* [44] performed a series of triamcinolone acetonide delivery experiments on rabbits under different circumstances: immediate euthanasia (no conjunctival or choroidal flow); with a 'conjunctival window' (no conjunctival flow but choroid intact); cryoablation of the choroid (conjunctival flow, but no choroidal circulation); and control (conjunctival and choroidal flow). The results showed that elimination of the conjunctival flow (including both blood and lymphatic flow) allowed significantly more drug to enter the vitreous, identifying it as a crucial clearance mechanism to overcome. Pontes de Carvalho *et al.* [20] sutured a reservoir to the sclera whose only exit was the scleral surface. They found significantly more delivery to the retina and vitreous from the implant versus from a simple injection and further determined that the improvement in delivery was amplified if the implant was sutured tightly enough to indent the sclera. Taken with Robinson's result, the Pontes de Carvalho experiment demonstrates that transscleral delivery will be most effective if external losses can be minimized.

6. Computer modeling

Because of the importance of intraocular drug delivery, numerous studies have been performed to predict biodistribution of drugs delivered by various methods (**Table 2**). Early work (e.g., [54,55]) used idealized geometric representations, limited by both available information and computational power. A major advance occurred in the mid-1990s when Friedrich *et al.* [56,57] used the finite-element method to implement realistic geometric representations, most obviously in that they accounted for the non-sphericity of the vitreous gel due to the presence of the lens. The realistic-geometry approach has since been used by others and models are starting to be verified against experimental data (e.g., [40]). A recent study [58] included an extremely detailed analysis of the consecutive barriers to transscleral delivery and the results of that study may eventually be combined with realistic geometry models to obtain a more accurate description of the transscleral delivery process.

Table 2. Modeling studies performed to predict the biodistribution of drugs delivered by various methods of intraocular drug delivery.

Ref.	Geometry	Source	Notes
[55]	Sphere	Injection (centre)	Highly idealized. Analytical solution
[72,73]	Spherical shells	Continuous (exterior)	Fit to experimental blood-vitreous transport data
[54]	Cylinder	Injection (centre)	Included metabolism of injected drug
[56,57]	Realistic (human/rabbit)	Injection (various)	Included elimination by aqueous humor First anatomically-based model
[74]	Realistic (human/mouse)	Controlled release (various)	Included aqueous humor permeation through vitreous Included square-root-of-time release kinetics
[75,76]	Realistic (rabbit)	Controlled release (various)	Accounted for loss to the choroidal circulation
[40,41]	Realistic (rabbit)	Controlled release (various)	Compared to MRI data in rabbit
[20]	One-dimensional (human/mouse)	Trannscleral	Very detailed one-dimensional analysis of barrier tissues No accounting for eye shape

MRI: Magnetic resonance imaging.

As better and better computer models emerge, the opportunity will arise to bring them to bear on specific problems. It is imperative, however, that the computer modelers do more than simply make predictions and verify them experimentally – the models must be used either to design new strategies, or to gain insight that could not be acquired directly by experiment. For example, *in vivo* studies are now giving us information about biodistribution of drugs with different chemistry. It would be difficult, if not impossible, to separate partitioning effects from diffusion effects via experiment, but a computer model could be used to extract the necessary thermodynamic and chemical parameters, which in turn could be used to predict distribution in humans based on experiments on animals.

7. Conclusions

Although the studies described above are broad and varied, there are four major conclusions that one can draw. First, the sclera itself is not a major barrier to the transport of most drugs of interest, even fairly large ones. This conclusion is not new, but merits emphasis because of its obvious necessity for the success of the delivery method. Second, we conclude from the *in vivo* studies that losses to the surrounding tissues, such as the conjunctival lymphatic system, must be minimized in order for transscleral delivery to be effective. Third, the preliminary *in vivo* studies shown in **Table 1** demonstrate that various delivery schemes are possible. At present, there is no clear best choice and different schemes may in fact be better for different drugs or diseases; now that the basic principles have been established, design and optimization can begin.

Finally, we observe that computer studies to date have provided good qualitative predictions, but have not, in general, been used to acquire new information or understanding, nor have they driven new experiments. As members of the computer modeling community, we recognize this considerable shortcoming of the work of ourselves and others and hope that models will soon reach the point where they move beyond 'academic exercise' status and become an integral part of the scientific and design processes.

8. Expert opinion

The enormous advantages of transscleral drug delivery make it the delivery method of the future. The critical question, however, is how long it will remain a method of the future and when it will actually be used clinically. To our knowledge, there have been no human sustained transscleral delivery studies and experiments on animal models remain relatively rare and only partially successful. Transscleral iontophoresis is less attractive than a controlled-release system because of the complexity of the iontophoretic device, but is a slightly more mature field. As such, it may represent an intermediate development – important in the near term – and an improvement over what is presently available, but eventually replaced by an entirely passive system that can be implanted and then managed periodically. Regardless, transscleral drug delivery will remain exploratory until we have a better understanding of the process.

Our understanding is undoubtedly improving and rapidly so. A few years ago, it was generally accepted that removal of drug by the choroidal blood flow would be a major concern, but now there is mounting evidence that external, not internal, losses predominate. However, there remain open questions that must be addressed before we can move forward as a community.

8.1 What is the role of the retinal pigment epithelium?

The RPE is clearly a significant barrier *in vitro* and presumably is significant *in vivo* as well (one might assert that, based on the import of the two barriers, transscleral delivery should be

called '*trans*-RPE delivery'). Less clear is the nature of the barrier, whether it affects different compounds differently, how much is due to active transport by the RPE cells (which would be expected to be asymmetric, consistent with some results) and how much is due simply to obstruction by the RPE cells. An additional question is whether *trans*-RPE transport is necessary if choroidal neovascularization is the primary target. Our understanding of the role of the RPE is still developing, and significant advances are expected to be made over the coming years. The reader is referred to [59] for a nice review of the RPE and other barrier tissues in the eye, with emphasis on the role of transport proteins.

8.2 How does chemistry affect biodistribution?

It is well known that charge and hydrophilicity are critical factors that determine the partitioning of drugs among different tissues (e.g., acid orange 8 showed a partition coefficient of 1.6 between water and the vitreous *in vitro* even though the latter is extremely hydrated [60]). Specific chemistry is also important, as demonstrated by the targeted systemic delivery schemes. Few studies have been performed on the effect of drug chemistry on biodistribution, with drugs chosen because of clinical relevance or for ease of detection (e.g., fluorescein). As new drugs appear, care must be taken in extrapolating results from previous studies, especially for systems with different fundamental chemistry.

8.3 How does species affect biodistribution?

Rats and mice have very small eyes compared with humans. Scleral thickness varies across species (e.g., [61,62]) and differences in circulatory structures could also be significant. Studies of biodistribution in animal models are extremely informative, but we must ask ourselves how well those ideas translate to humans. It is further necessary to recognize that animal models usually have an intact vitreous, but most patients for AMD, being elderly, have a highly liquefied vitreous.

8.4 How can delivery rate (and perhaps location) be optimized and managed?

At present, transscleral delivery is still in its infancy and, thus, no system is able to deliver as much material as the physician would like. However, as the questions above are resolved and technology improves, the potential for high-efficiency transscleral drug delivery will be realized. Critical secondary questions will arise – how can we determine the appropriate dose so as to maximize medical value without toxicity? How close to the macula must a source be? A design that gives less total delivery,but greater localization and dose control, for example, might be unattractive now, but could suddenly become more attractive if an effective but toxic (in high doses) drug were to become available.

It is our opinion that these questions will be answered by two parallel strategies. Thoughtful and creative experiments have been used to identify important phenomena and clearly there must, and will, be further studies, hopefully targeted specifically at elucidating and quantifying the relevant effects. In complement, computer modeling has the potential to provide information that cannot be measured experimentally or to provide new insights into phenomena that can be studied only indirectly by experiment.

Declaration of interest

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