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editorial

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Ocular drugs and drug delivery systems — Current trends and future perspectives

Just having returned from one of the largest eye research conferences, it is the perfect time to write this editorial. So much has happened in this area over the past two decades with research no longer restricted to well-known drugs and simple delivery systems. Many novel targets are being investigated to treat anterior and posterior segment diseases and while contributions on drug delivery systems were once a rarity, there is now a plethora from which to choose. However, does this mean that we have found the 'Holy Grail' to treat ocular conditions yet? No, it certainly does not.

Many knowledge gaps still exist, whether on the predominant pathways involved in a certain ocular disease, or on the optimal design of sustained delivery systems. But why is it so difficult to adapt such systems to the eye when they have been used successfully in other parts of the body? One of the major hurdles remains the molecule size restriction, limiting most drug-device combinations to potent small molecules such as steroids and prostaglandin analogues, but becoming problematic for macromolecules. Other knowledge gaps include (i) a general lack of ocular drug pharmacokinetics knowledge due to the inability of sampling posterior segment tissues in humans; (ii) the unknown ocular safety profile of materials used in sustained release systems; and (iii) the limited availability of preclinical models that allow adequate translation from the bench to the bedside.

This special issue is dedicated to addressing some of these knowledge gaps with contributions ranging from feature articles to foundation reviews covering a variety of novel drug targets and delivery technologies for anterior and posterior segment diseases. Beginning with the front of the eye, Markoulli and Hui [1] are discussing emerging targets to manage inflammation and promote tear secretion in dry eye disease, a condition that effects over 30 million people in the United States alone and has long been underdiagnosed and undertreated. The recent TFOS DEWS II report defines dry eye disease as "*a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles,*" highlighting that tear supplementation alone is insufficient. Much lower in incidence, but by no means less important, are rare corneal diseases covered in the review by Jimenez et al. [2] Developing therapeutics for "orphan" diseases, which are defined by the FDA as "*a disease or disorder affecting fewer than 200,000 people in the United States*", offers a number of advantages including special tax credits and smaller patient numbers required for clinical trials. Thus, there is great potential for the reformulation of already existing drugs for such rare conditions.

Even for other ocular conditions though, novel drug delivery systems or drug-device combinations offer great opportunities, especially

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when using already FDA approved drugs with well-known safety and efficacy. As such, it is no surprise that the number of research groups and companies working on novel drug delivery systems has skyrocketed over the past decade, with many combination products currently in clinical trials. However, to be marketed successfully such combination approaches need to achieve clear advantages over the drug alone especially with regard to therapeutic efficacy, lowered toxicity and increased patient compliance. This gap between the need and the number of approved novel ocular drug delivery technologies is covered in a feature article by Neumann and Barequet [3], who firstly describe the medical need for such systems, before summarizing currently available retinal delivery technologies on the market. The authors then offer their opinion on promising delivery technologies currently in the pipeline before pointing out some of the bottlenecks that limit translation of innovative technologies into commercial products.

Novel delivery systems, including hydrogels, nanoparticles, liposomes and intraocular implants are reviewed in a number of articles in this issue, but why is it that hardly any of these technologies have made it to the market? Subrizi et al. [4] discuss the importance of drug payload, release rate and material properties when designing an ocular drug delivery system. Covering physical tissue barriers in the eye as well as dosing considerations, this article offers a user-friendly toolbox for early stage design of an ocular drug delivery system without expertise in kinetic modelling. Nevertheless, with the inability to perform in-depth pharmacokinetic studies in the clinical setting, pharmacokinetic modelling still plays an important role in the development of new ocular drugs and drug delivery systems. This is highlighted in the articles by Missel and Sarangapani [5] and Gukasyan et al. [6], covering computational modelling methods to assess the safety and efficacy of long-acting delivery technologies. Safety is also a concern in the article by Thackaberry et al. [7] which describes the considerable challenges for designing long-acting delivery systems for the eye, especially for biologics, that are well-tolerated by the ocular tissues.

The question remains whether the development of the perfect delivery system is sufficient or whether new drug targets and delivery routes also need to be investigated. Intravitreal injection of the drug-containing solution has long been the gold standard to treat retinal conditions. And while this route delivers the drug close to the target site, there are volume restrictions and the drug is cleared relatively fast. Moreover, injected drugs may have difficulty in reaching the outer retinal layers as well as the choroid. In these cases, alternative delivery routes may offer an advantages such as injection into the suprachoroidal space covered by Jung et al. [8] or application of depot formulations into the periocular region discussed by Agban et al. [9] However, these may still be inefficient when treating genetic diseases affecting the retinal pigment epithelium or the photoreceptors. Here, viral or non-viral vectors as described by Bordet and Behar-Cohen [10], as well as specific delivery technologies able to cross the blood–retinal-barrier as discussed by Himawan et al. [11] might be required. Finally, this special issue would not be complete without reviewing prominent posterior segment diseases including their current management as well as novel disease targets such as the P2X7 receptor covered by Fletcher et al. [12] or Connexin43 hemichannels reviewed by Mugisho et al. [13] which, with the recent resurgence of the inflammasome pathway in many ocular conditions, have gained increasing attention.

So what are the perspectives for the future of ocular drugs and drug delivery? As exemplified by the articles in this special issue, we will likely see therapeutics allowing for longer dosing intervals, more technical options for drug delivery and novel molecular entities. And while macromolecules were once the future, the trend seems to be reversing to novel smaller molecules that enable higher payloads and have longer in vivo stability. In summary, this issue incorporates advances in ocular drugs and drug delivery technologies for both anterior and posterior segment disease, while highlighting the current challenges faced with regards to translating these into clinically successful products. We therefore hope that our readers will find this volume comprehensive and highly resourceful for the development of ocular therapeutics. This special issue would not have been possible without the timely submission and revision of articles by the authors, critical evaluations by the reviewers and the editorial assistance provided by Ms. Pien van Spijker-Laumanns and Ms. Bharathi Sims, as well as other staff at Elsevier who ensured that papers were carefully processed, reviewed and published to their deserved high standard. We are also thankful to Dr. Steve Carney, Editor-in-Chief, for providing us the opportunity to develop this theme issue. We hope you enjoy reading this special ocular drugs and drug delivery issue – to us it is more than meets the eye!

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