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Keep your eyes open: challenges and opportunities in Ophthalmic Therapeutics

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The eyes are our windows to the world. Major ocular diseases, including cataracts, glaucoma, age-related macular degeneration (AMD), diabetic retinopathy (DR), dry eye syndrome and allergic conjunctivitis, can cause vision impairment and even blindness, which not only affect our daily life, but also have a significant socio-economic and psychological impact on our society. The prevalence of vision impairment was estimated to be 147 million people in 2010, and is projected to reach 191 million in the world in 2020 due to an increase in aging populations. The market for ophthalmic disease therapeutics is expected to reach \$18.7 billion this year, and is predicted to grow steadily. Ophthalmic drug development has been in the forefront of therapeutic research partly because the eye is an accessible and immunologically isolated organ, which has the advantage of avoiding the complications of systemic drug delivery. With the recent advances in genetics, genomics and stem cell biology, the mechanisms of many ophthalmic diseases are being increasingly revealed. Accordingly, the field of ophthalmic therapeutics is facing unprecedented challenges and opportunities.

Looking back in history, ophthalmic drug development has been driven by the scientific breakthroughs. For example, the discovery that vascular endothelial growth factor (VEGF) is a driving force of choroidal neovascularization in AMD has led to the successful development of anti-VEGF antibodies for wet AMD therapy. The discovery that prostaglandin mediates reduction in intraocular pressure (IOP) has led to the treatment of ocular hypertension in glaucoma using prostaglandin analogues. Research over the past decade has uncovered novel mechanisms for many ocular diseases, which will likely spawn new therapeutic solutions. But this field is not without challenges: (A) currently there is no cure for many ocular diseases, including dry AMD, DR and glaucoma; (B) current ophthalmic drug development is not based on the unique characteristics of ocular diseases,

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but mainly applies agents developed for non-ocular diseases to the eye; (C) most of the ocular diseases are multi-factorial diseases with both genetic and environmental (nutritional) risk factors, therefore many drugs only work for a subset of patients. For example, cyclosporine, acting as an immune-modulator for dry-eye disease, is only effective in about 15% of all patients; (D) ophthalmic drug delivery, especially to the posterior eye, remains a considerable challenge. These challenges present unique opportunities for researchers in the field of ophthalmology to further elucidate the mechanisms of and develop innovative therapeutics and delivery approaches for ocular diseases.

Despite the challenges, significant progress has recently been made towards understanding the mechanisms of several ocular diseases, which may translate into future therapeutics. Dry AMD accounts for up to 90% of the AMD cases and is currently without cure.

Polymorphisms in members of the complement system, especially complement factor H (CFH), have been associated with AMD. Moreover, CFH was recently shown to protect against oxidative stress-induced inflammation in animal model. Inhibitors of the complement system and the recombinant form of CFH are being tested preclinically for AMD treatment. A β amyloid, originally implicated in Alzheimer's disease, was recently associated with pathogenesis of AMD. Anti-A β amyloid antibody has shown promise in animal models of AMD. Autophagy is currently being investigated for AMD involvement, and may represent a potential therapeutics for AMD (See review in this issue). Diabetic retinopathy is one of the leading causes of blindness in the working class. Besides laser photocoagulation and vitrectomy surgery, several therapeutic options, including protein kinase inhibitors, cyclooxygenase inhibitors, anti-VEGF and slow release steroid, are on clinical trials. Some of them may enter the market in the near future. As reviewed in this issue, pericytes and the angiopoietin (Ang)-Tie-2 signaling also play an important role in the development of DR, and may be potential therapeutic targets for DR. For glaucoma, the current mainstay for treatment is to lower IOP, therefore preventing further damage to the optic nerve. β -blocker, prostaglandin, carbonic anhydrase inhibitor, miotics, α -adrenergic agonist, or their combinations are routinely used for lowering IOP. Rho kinase inhibitors and actin depolymerization agents are currently tested in clinical trials for safely reducing IOP. Dominant mutations in the olfactomedin (OLF) domain of myocilin have been associated with several populations of familial glaucoma, and molecular studies suggest that the OLF domain of myocilin may be a bona fide target for future glaucoma therapeutics (reviewed in this issue).

Looking into future, the explosion in basic research in ocular biology and disease will lead to revolutionarily innovative ophthalmic therapeutics. Numerous opportunities also present themselves to researchers working on medicinal chemistry, new biomaterials, and new delivery system (see reviews for these subjects in the issue). With the coordinated effort of all these groups, the future of ophthalmic therapeutics is bright.

In this issue

This issue features a selection of mini-reviews on the current research that may lead to future ophthalmic therapeutics. Cai *et al.* review the role of pericyte-endothelial interaction and the angiopoietin (Ang)-Tie-2 signaling in diabetic retinopathy (DR), as well as the

potential of targeting of pericytes through Ang-Tie-2 signaling for DR therapeutics. Harkin discusses the potential of using silk fibroin as a new biomaterial for corneal reconstruction. Basavarajappa and Corson describe the role of KLF14 oncogene in the development and progression of retinoblastoma (RB), and predict KLF14 as a potential drug target for RB. Kaarniranta *et al.* summarize the role of autophagy in age-related macular degeneration (AMD), and discuss the use of autophagy regulating kinases as potential therapeutic targets for AMD. Kador et al discusses the unique needs and opportunities for medicinal chemists in ophthalmic therapeutics. Donegan and Lieberman describe myocilin as a bona fide drug target for glaucoma, and discuss the targeting of the olfactomedin (OLF) domain of myocilin for glaucoma drug development. Sheardown and Chauhan reviewed the challenges and prospects for drug delivery in ophthalmic therapies.

We cordially invite you to enjoy the focused issue of ophthalmic therapeutics.

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