New visions in ophthalmic drug development

Over the last 10 years we have seen the introduction of several new 'ophthalmology only' pharmaceutical products emerge such as Trusopt (dorzolamide, Merck) and Xalatan (latanoprost, Pharmacia). Innovative products such as these have driven much of the ophthalmic pharmaceutical growth, outpacing the older products that were often developed for ophthalmology via other therapeutic areas. With the ophthalmic pharmaceutical sector currently at around $5 billion worldwide, the continued growth is likely to be driven by even more first-in-class entries in ophthalmology. Two areas that are especially poised for explosive growth are dry eye and retinal disease, in which many new therapeutic approaches are currently in development.

By Dr Benjamin R. Yerxa, Dr Ward M. Peterson and Robin S. Whitsell

Recent changes and restructuring in corporate aspects of the ophthalmology marketplace will likely influence the future of ophthalmic drug discovery. For example, in 1999 Bausch and Lomb, a company with few proprietary prescription products, restructured itself by selling its Miracle Ear hearing aid, Charles River and Ray Ban divisions. It then essentially used the proceeds to purchase the European-based eye care company Groupe Chauvin for $228 million in cash. This movement helped to reposition Bausch and Lomb for growing its global prescription drug business. In July 2002 Allergan spun out its optical medical device business to create Advanced Medical Optics, transforming Allergan into a specialty pharmaceutical 'pure play'. On March 21, 2002 Nestle spun out Alcon in an IPO valued at about $2.3 billion, creating the world's largest independent eye care company. Other transactions have raised attention, such as the start-up financing of EyeTech, which raised $100 million for a 'biotech' anti-angiogenesis project for treating retinal disease in August 2001. Other biotechnology and pharmaceutical companies, such as Genentech, Inspire, ISTA and Eli Lilly have invested significant cash and resources into their advanced stage ophthalmic products. Shifts like these in ophthalmic pharmaceutical R&D are shaping the future of eye care.

Emerging areas

Several disease areas of ophthalmology are under-served by prescription pharmaceuticals. The largest unmet medical needs are dry eye disease and a number of retinal diseases, such as age-related macular degeneration, diabetic retinopathy and retinitis pigmentosa. These conditions have been under-served primarily because of their complex etiology and progression, which has eluded the development of new drugs. In recent years, insight

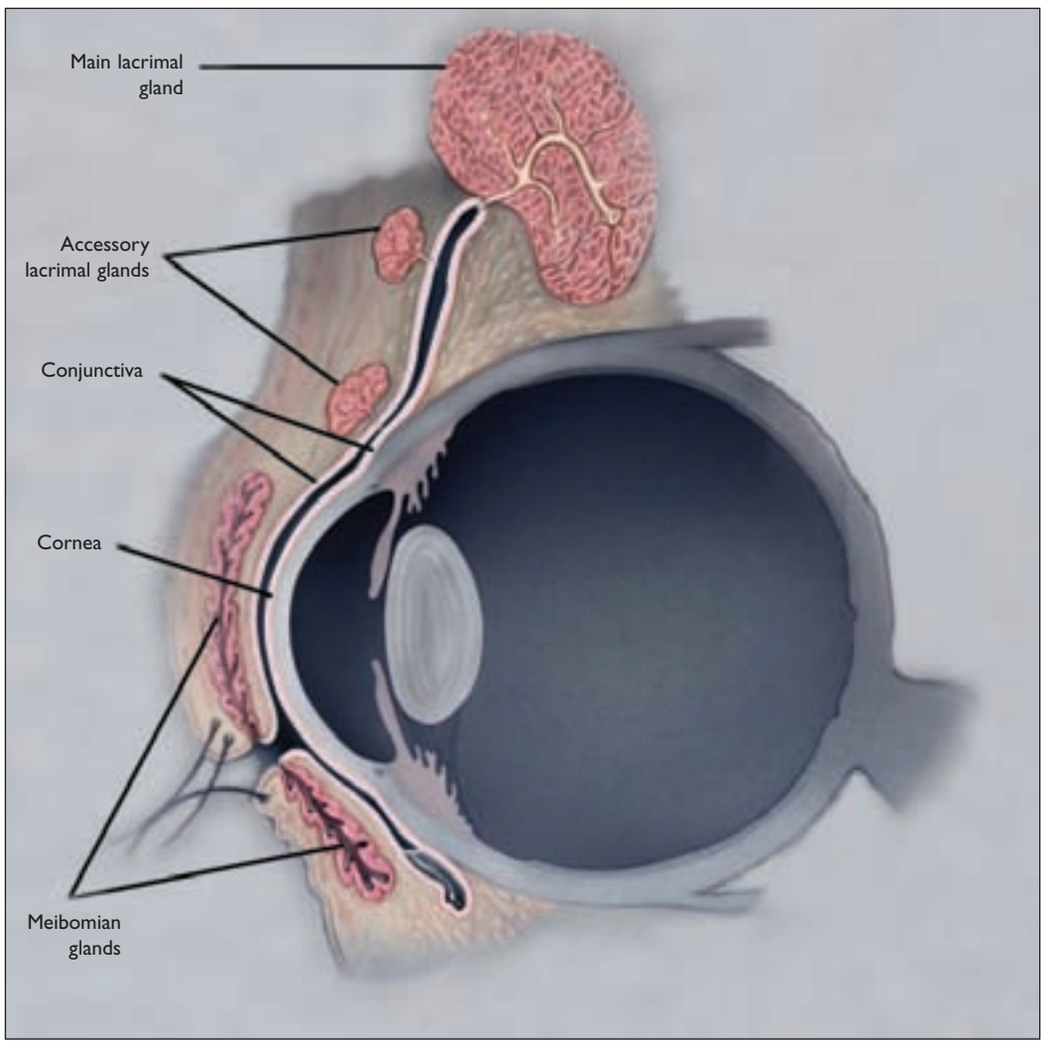

Figure 1
Cross-section of the eye highlighting ocular surface structures. The eye seen in cross-section reveals the main and accessory lacrimal glands that secrete bulk fluid and proteins, and the meibomian glands in the eyelids that produce lipids. The conjunctival surface joins with the cornea and surrounds the inner eye lids, producing mucus and additional fluid to directly hydrate the ocular surface

into disease mechanisms and identifiable drug targets has resulted in the emergence and development of a number of promising drug candidates that are now in late-stage clinical studies, particularly for the treatment of dry eye disease, age-related macular degeneration and diabetic retinopathy.

Dry eye

Dry eye syndrome is a multifaceted disease characterised by symptoms of chronic irritation and inflammation (itching, burning, pain and gritty sensations) and ocular surface damage (as evidenced by corneal and conjunctival staining)[4]. The health and integrity of the ocular surface are maintained by the fluid and protein secreting main and accessory lacrimal glands, the lipid producing meibomian glands and the fluid and mucin secreting conjunctival epithelium (**Figure 1**). Epidemiological studies of dry eye show an increased prevalence in post-menopausal women, effecting as many as 12 million people in the US alone[1]. Despite the numerous over-the-counter artificial tears available as tear substitutes, these aqueous lubricant solutions provide short-lived relief of symptoms, but do not address the underlying problems associated with the disease, nor do they have significant effects on ocular surface health. Currently there are no approved, pharmacologically active drugs for treating dry eye disease; however, recent approaches to treating dry eye disease in clinical development include targeting inflammation, secretion and hormones.

Anti-inflammatory

A major component of dry eye disease is the persistent ocular surface inflammation that occurs, either primarily due to autoimmune diseases such as Sjögren's syndrome, or secondarily as a result of chronic dryness and irritation. Regardless of the cause, inflammatory infiltrates release cytokines

that accumulate on the ocular surface and slowly degrade and remodel the epithelium, leading to the hallmark sign of dry eye: a compromised ocular surface that can be assessed by corneal and conjunctival staining techniques. Anti-inflammatory interventions have shown some promising results.

Restasis (cyclosporine A, Allergan), a topical immunosuppressant that reduces ocular surface inflammation, is currently undergoing a Phase 3 clinical trial to confirm positive results from previous Phase 3 trials[2]. Allergan received an approvable letter from the FDA on August 24, 1999 and expects to launch Restasis in late 2003. In November 2002, Debiopharm announced that a more water-soluble prodrug of cyclosporine A may be developed as a treatment for dry eye. Another anti-inflammatory drug that is used systemically for similar indications as cyclosporine, called FK-506 (tacrolimus, Fujisawa), is being developed outside Asia for dry eye disease by Sucampo Pharmaceuticals. Tacrolimus for treating dry eye disease is currently in Phase 2 in Europe with plans for future US studies in the coming years.

Topical corticosteroids, although generally contraindicated for chronic use due to the risk of increases in IOP and cataract formation, have been used as 'pulse therapy' in which dosing is continued for only several days or a few weeks at a time. In Sjögren's disease patients, non-preserved corticosteroid treatment resulted in a desired decrease of corneal staining and a resolution of filamentary keratitis. Some patients also experienced relief from the symptom of irritation[3].

Secretagogues

Since dry eye is a disease of impaired ocular surface hydration as measured by a marked decrease in tear secretion particularly from the lacrimal glands, it is reasonable to expect that a pro-secretory approach would be beneficial. Despite the obviousness of such an approach, secretagogue-based therapeutic development for dry eye has not been successful. For example, muscarinic secretagogues (M3 receptor agonists) approved for dry mouth, such as Salagen[4] (pilocarpine, MGI) and Evoxac[5] (cevimeline, Daiichi), have not been proven efficacious in treating dry eye. This may be due in part to the multiple components of ocular surface secretion, ie it is a combination of glandular and epithelial secretion that is under both neural regulation and nonadrenergic, noncholinergic control.

The most advanced secretagogue in clinical development is INS365 Ophthalmic Solution (diquafosol, Inspire), a P2Y2 nucleotide receptor

Table 1: Dry eye medications in development

COMPANY	COMPOUND	TYPE OF MEDICATION	PRESUMED PHASE OF DEVELOPMENT
Alcon	15-HETE	Secretagogue	Phase 2
Allergan	Restasis	Anti-inflammatory	Phase 3
Allergan	Androgen Tear	Hormone	Phase 3
Inspire	INS365	Secretagogue	Phase 3
Otsuka	OPC-12759	Secretagogue	Phase 2
Sucampo	FK-506	Anti-inflammatory	Phase 2

Table 2: Wet AMD medications in development

COMPANY	COMPOUND	MEDICATION TYPE	PRESUMED PHASE OF DEVELOPMENT
Alcon	Anecortave Acetate	Steroid subtenons injection	Phase 3
EyeTech	Macugen	Anti-angiogenesis intravitreal injection	Phase 3
Genaera	Squalamine	Anti-angiogenesis	Phase 1
Genentech	RhuFab	Anti-VEGF intravitreal injection	Entering Phase 3
Miravent	SnET2	PDT	Post-Phase 3
Oxigene	Combretastatin	Vascular targeting agent	Entering Phase 1/2
Novartis, QLT	Visudyne	PDT	Approved

agonist. This nucleotide stimulates primarily conjunctival epithelial secretion of salt, fluid and mucin and possibly lipid secretion from the meibomian gland, thereby making up the principal layers of the tear film. The conjunctival secretion can be stimulated with INS365 to provide normal tear volumes even in animals in which the lacrimal glands have been removed[6]. INS365 is currently in Phase 3 clinical testing in the US, although the company recently reported that the FDA would consider an NDA filing based on the completed studies to date. Inspire expects to launch INS365 in the US in early 2004 with its partner Allergan.

Several mucin secretagogues are being developed for dry eye therapy. OPC-12759 (Rebamipide, Otsuka), a gastric protectant approved in Japan, is currently in Phase 2 in the US and is reported to work via upregulation of mucin secretion and/or proliferation of mucin-containing goblet cells[7]. 15-HETE, an intermediate in the arachidonic acid cascade, is being developed by Alcon as a dry eye treatment and is reported to work via direct stimulation of mucin secretion[8]. 15-HETE appears to be in Phase 2 in the US, although results of patient trials have not been reported yet.

Hormone replacement

Since dry eye is most common in post-menopausal women, the link to hormonal changes has been studied extensively. Hormone replacement therapy by itself, however, has not been correlated with decreased dry eye. In fact, the opposite appears to be true[9]. Despite the epidemiological puzzle, researchers at the Aborn Eye Research Center in New York, are currently investigating a proprietary topical estradiol eye drop and have obtained positive, preliminary results from a small, single-centre, placebo-controlled Phase 2 trial in patients with dry eye[10].

Decreases in androgen hormone levels are also observed in post-menopausal women and in Sjögren's syndrome and are correlated with decreased glandular secretion. It has been postulated that this hormone imbalance is responsible for drying of mucosal surfaces throughout the body as women age. For the eye, a decrease in

androgens may lead to dysfunction of the oil producing meibomian glands in the eyelids (**Figure 1**). Since the outermost oily layer is responsible for providing tear film stability and preventing evaporative loss of water, abnormalities in meibomian gland function lead to 'evaporative' forms of dry eye[11]. The relationship between this as it relates to dry eye disease is being studied in dry eye patients (Androgen Tear, Allergan). Interestingly, a topical androgen gel is being developed for vaginal dryness associated with menopause, and positive results from patient trials have been reported (Tostrell, Cellegy).

Diseases of the retina

Corneal diseases, although debilitating, are not the leading causes of blindness. Conditions affecting the retina, including classically inherited ones and those secondary to systemic diseases, are the culprits in the industrialised world. Primary among these diseases, according to a March 20, 2002 NEI press release, more than 5.3 million Americans are affected by diabetic retinopathy, which predominantly affects central vision. An additional 1.6 million Americans over 60 years of age have age-related macular degeneration, another disease that destroys central vision[12]. In addition, approximately 1 in 4,000 worldwide is afflicted with perhaps the most debilitating of all inherited blinding diseases, retinitis pigmentosa. Hence, retinal diseases such as age-related macular degeneration (AMD), diabetic retinopathy (DR) and retinitis pigmentosa (RP) represent by far the largest areas of unmet medical needs and untapped pharmaceutical markets in ophthalmology in industrialised nations.

Recent advances in the understanding of the underlying pathophysiology of AMD, DR and RP have paved the way for the development of potential new drugs for halting or slowing the progression of vision loss associated with these diseases. Although wet AMD and DR are very different diseases with unrelated etiology, there has been an emerging appreciation that similar vascular abnormalities (namely leakage and proliferation of choroidal blood vessels in wet AMD and leakage and proliferation of retinal blood vessels in diabetic retinopathy) play key roles in the symptomatic progression of both diseases.

Age-related macular degeneration

AMD is the leading cause of blindness in people over 60 years of age in industrialised nations[13]. Most patients have non-symptomatic AMD, which can usually be diagnosed by an ophthalmologist or optometrist during a routine eye examination. AMD is classified as dry or wet, depending on whether there is fluid exudation arising from leaking and proliferating choroidal blood vessels. Although 90% of patients with AMD present with the dry form, actual blindness associated with AMD is predominantly due to the wet form. Nearly 200,000 people are blinded by AMD each year, and because of the increasing elderly population, it is estimated that there may be up to 500,000 new cases of blindness yearly in the US by the year 2030 given the current standard of therapy. There are essentially three modes of treatment developed or in development for treatment of wet AMD: photodynamic therapy (PDT), steroid therapy and anti-VEGF therapy. All other medications in development are outside of these models.

Photodynamic therapy (PDT)

The theory behind photodynamic therapy is to create scarring at the precise area of neovascularisation (the inappropriate leakage and proliferation of blood vessels). The patient is given a drug that is intended to make blood vessels and specifically neovascular areas photosensitive. Upon applying light via laser to those now sensitised areas, the underlying tissue will be destroyed effectively cauterising the leakage. The only approved drug for the treatment of wet AMD is based on this principle. Visudyne (Verteporfin, Novartis/QLT) was approved in the US in April 2000 for a minor subset of wet AMD. It is administered intravenously in its inactive form, where it is thought to accumulate very specifically in choroidal neovascular cells. Following intravenous administration, a low-energy laser is used to activate the drug, which leads to the subsequent closure of the leaky blood vessels. Patients treated with Visudyne require treatment up to four times a year. PhotoPoint SnET2 (Miravent) is another PDT treatment under clinical investigation. Analysis of two completed pivotal Phase 3 clinical trials for in January 2002 showed that the drug did not achieve statistical significance in primary efficacy endpoint. However, the Phase 3 results for PhotoPoint SnET2 are currently being evaluated for efficacy in smaller subset populations of AMD patients.

Anti-angiogenesis: anti-VEGF

There is now very strong evidence that vascular endothelial growth factor (VEGF) protein plays a predominant role in the progression of wet AMD and diabetic retinopathy. VEGF is a secreted signalling protein that is required for normal development of the vasculature in the body. However,

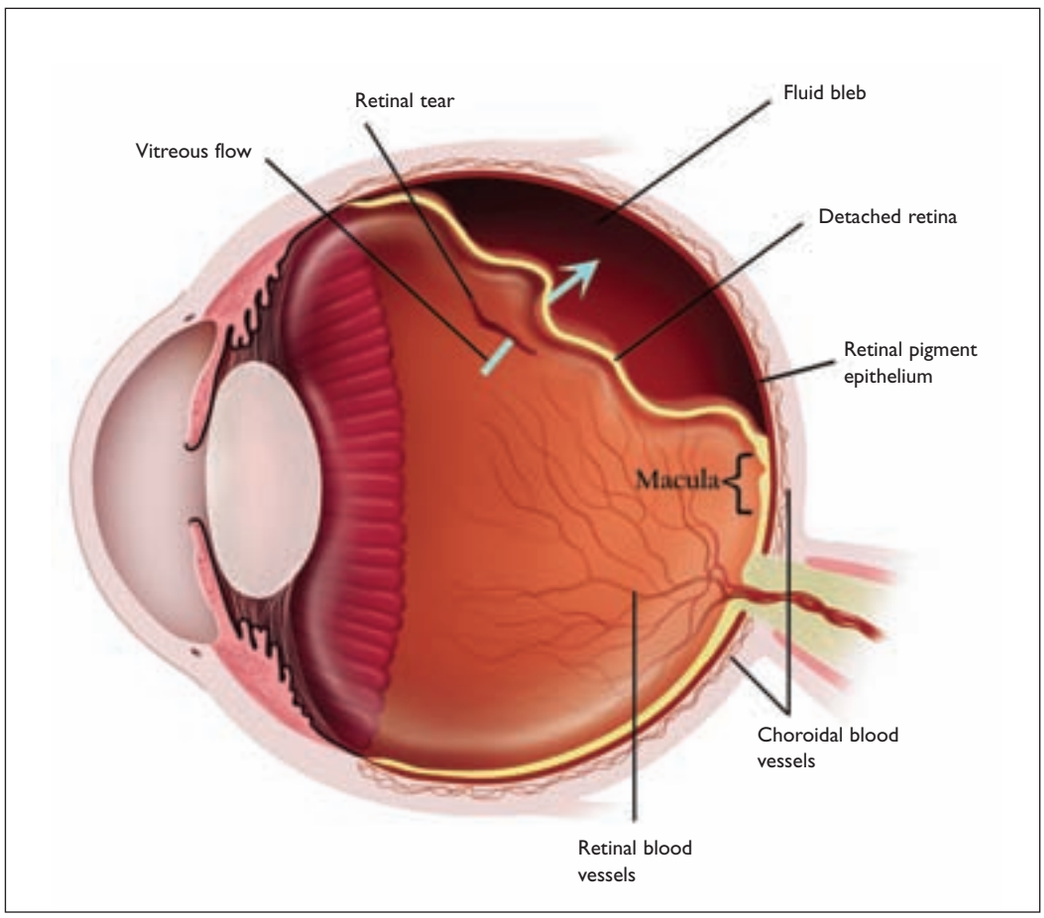

Figure 2
Cross-section of the eye highlighting posterior structures. A rhegmatogenous retinal detachment is pictured in the upper hemisphere, where a single retinal tear results in the accumulation of vitreal fluid between the retina and retinal pigment epithelium. Other notable structures include the choroidal blood vessels and retinal blood vessels. Proliferation and leakage of choroidal blood vessels behind the macula results in 'wet' AMD. Leakage and proliferation of retinal blood vessels result in diabetic retinopathy

VEGF stimulation and signalling in diabetic retinopathy and wet AMD causes otherwise stable and mature endothelial cells to become leaky and proliferate in a process generally referred to as pathological angiogenesis. Pathological angiogenesis is also seen in the development of many types of tumours, which secrete VEGF to stimulate the local growth of new blood vessels to nourish the tumour. Putative anti-angiogenic therapies (particularly anti-VEGF approaches) in development for tumour regression are thought to be applicable for potentially treating angiogenic diseases of the retina (and vice-versa). Multiple approaches that disrupt VEGF signalling are currently in clinical or late-stage preclinical ophthalmic drug development. The most advanced of these compounds in clinical development for wet AMD is the aptamer Macugen (Pegaptanib sodium, Eyetech)[14], which has completed enrollment in two pivotal Phase 3 trials as of August 2002. An additional anti-VEGF monoclonal antibody for wet AMD completed a Phase 1b/2 study in September 2002, rhuFab V2 (Ranibizumab, Genentech)[15]. Phase 3 enrollment for rhuFab V2 will reportedly begin in 2003.

Anti-angiogenesis: other approaches

Another new anti-angiogenic treatment under development for wet AMD is an angiostatic steroid, Anecortave Acetate (Alcon)[16]. Anecortave Acetate has been shown in Phase 2 studies to be effective in preserving vision and is currently in Phase 3 studies. Anecortave Acetate is given bi-annually as sub-tenon injections near the exterior part of the back of the eye. This administration route and the frequency of dosing are less invasive and much less frequent than the intravitreal injection regimens that are required for delivery of Macugen and rhuFab V2. A less selective, corticosteroid approach, in which a sustained release pellet containing dexamethasone is implanted inside the eye, is being investigated for the treatment of diabetic macular edema and is currently in Phase 2 trials (Posurdex, Oculex).

The aminosterol squalamine (Genaera) is another anti-angiogenic compound that inhibits VEGF-induced, as well as other growth factor-mediated, endothelial cell activation, proliferation and migration. Systemic administration of squalamine was shown to be effective in inhibiting ocular neovas-

cularisation in various preclinical models. Genaera initiated a Phase 1/2 study in August 2002 for evaluating squalamine in patients with wet AMD. Combretatstatin (CA4P, Oxigene), a novel anti-angiogenic compound that specifically destabilises microtubules of newly formed endothelial cells, is also expected to enter into a Phase 1/2 study in patients with wet AMD in the near future.

P2Y2 receptor agonist

Since pathological accumulation of intra-retinal or sub-retinal fluid is a common feature and cause of visual loss in diabetic retinopathy, wet AMD and in a variety of other retinal diseases, such as cystoid macular edema, retinitis pigmentosa, central serous retinopathy and retinal detachment, it is thought that directly removing this fluid build-up may offer therapeutic benefit. Stimulation of fluid transport across the retinal pigment epithelium, a layer of cells juxtapositioned between the retina and the choroidal blood supply, has been demonstrated in animals by activating the P2Y2 receptors. This is expected to remove fluid from intra-retinal and subretinal spaces (**Figure 2**). A P2Y2 receptor agonist (INS37217 Intravitreal Injection, Inspire) is currently in clinical development using this novel approach for removing fluid build-up. A Phase 1/2 study was recently completed for INS37217, given as a single intravitreal injection, to patients with rhegmatogenous retinal detachments and enrollment in a Phase 2 study is expected to begin in 2003.

Diabetic retinopathy

Diabetic retinopathies, such as diabetic macular edema (DME) and proliferative diabetic retinopathy (PDR), are the leading cause of blindness in Americans under 60 years of age. Diabetic retinopathy accounts for an estimated 12% of new cases of blindness each year. There are an estimated 65,000 new cases of PDR and 75,000 new cases of DME annually in the US alone. The current standard treatment for PDR is laser photocoagulation, causing micro-burns on the retina that effectively cauterise the bleeding vessels but also inactivate the photoreceptors in that area. No medication is currently approved for DR.

Many of the same compounds that are being developed for wet AMD are also being studied in PDR, notably Visudyne. In addition, anti-angiogenesis compounds are also being explored. A number of studies have shown that the immediate downstream effects of VEGF signalling in microvascular endothelial cells, including those of the retinal vasculature, is predominantly mediated by protein kinase Cß (PKCß). Thus inhibition of PKCß may offer a novel approach for treating diabetes-induced microvascular complications, including DR and peripheral neuropathy. An oral medication based on this approach, LY-333531 (Eli Lilly), is in late stage clinical development for the treatment of DME and PDR. It is anticipated that filing for regulatory approval of LY-333531 for diabetic retinopathy in Europe will occur in 2003. Also, a somatostatin analogue, Sandostatin (octreotride, Novartis), has been shown in multiple clinical studies to provide various patient benefit outcomes in DR. The underlying mechanism of action is not fully understood, but may involve vascular anti-permeability and anti-proliferative effects owing to inhibition of growth hormone activity.

An additional complication in PDR is vitreous haemorrhaging, which is a major cause of visual loss for the patient. Vitrase (hyaluronidase, ISTA) has completed Phase 3 studies for evaluating the efficacy in the resolution of vitreous haemorrhage. Although primary efficacy was not reached in the Phase 3 studies, secondary analysis demonstrated improvement in visual outcomes following treatment and currently NDA approval is being sought.

Retinitis pigmentosa

Retinitis pigmentosa (RP) is the most common class of inherited photoreceptor degenerative diseases and affects approximately 1:4,000 worldwide. An estimated 100,000 to 200,000 Americans have RP, which is a genetically heterogeneous disease generally characterised by similar phenotypic manifestations: loss of peripheral vision followed by loss of central vision. Some RP patients suffer complete blindness. No drugs are specifically approved for RP. On-going approaches in development for inducing retinal neuroprotection (see below) may lead to new developments in RP, as may various gene or protein-based approaches currently in preclinical development. These include: ribozyme gene therapy, cell-based delivery of ciliary neurotrophic factor (NT-501, Neurotech) and gene-based delivery of pigment epithelium-derived factor (PEDF). PEDF has been shown to promote photoreceptor survival and inhibit ocular angiogenesis, and is currently being tested in Phase 1 (AdPEDF, GenVec) in AMD patients.

Neuroprotection

Therapeutic approaches that confer direct neuroprotection of retinal neurons remain perhaps the most elusive to develop. If effective at prolonging survival and function of retinal ganglion cells and photoreceptors, a neuroprotective drug may be

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used to treat diseases such as glaucoma, wet and dry AMD, retinitis pigmentosa, cone-rod dystrophy and a variety of photoreceptor-specific degenerations. An oral NMDA receptor antagonist (memantine, Allergan) is in Phase 3 clinical testing for glaucoma/neuroprotection. Memantine is already approved in Europe for the treatment of moderately severe to severe Alzheimer's disease[17]. There has also been a great deal of animal research around alpha-2 adrenergic agonists as potential neuroprotective agents and it is speculated that Alphagan (brimonidine, Allergan) is in Phase 2 clinical trials for this application.

Conclusions

It is evident that the future holds a wealth of opportunity for innovative ophthalmic drug discovery and development. Within the next few years, new treatments in major unserved areas are likely to emerge, such as INS365 Ophthalmic Solution for dry eye disease (diquafosol, Inspire) and Macugen for age-related macular degeneration (pegaptanib sodium, Eyetech). As our understanding of the underlying genetics and pathophysiology of ocular disease increases, more drugs will be developed primarily and specifically for ophthalmology. There are already striking examples of biotech, specialty and big pharmaceutical companies either repositioning themselves, or entering ophthalmology for the first time, after seeing a glimmer of these untapped treasures. Xalatan (latanoprost, Pharmacia) and Visudyne (verteporfin, Novartis/QLT) have demonstrated that as newer, better drugs enter the market, the chance of an ophthalmic blockbuster grows. These opportunities will not only provide patients with much needed first-in-class medicines, but will also provide the global ophthalmic pharmaceutical market with the potential to nearly double in size by the end of the decade.

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