Therapeutics

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The ophthalmic research generating the most “buzz” over the past two decades has been for neovascular retinal disorders with consecutive approvals of incrementally improving therapies. In the year 2000, photodynamic therapy (PDT) with verteporfin replaced laser photocoagulation for treatment of wet age-related macular degeneration (AMD), and this quickly became the standard of care, while still leaving huge opportunity for better treatment options. PDT did nothing to improve vision and showed only limited success for select patients in maintaining the vision loss that had already occurred at the time of therapy6,30.

So on came the vascular endothelial growth factor (VEGF) inhibitors 33, led by the approval in 2004 of pegatanib sodium injection for wet AMD which briefly replaced PDT as the standard of care. This was subsequently unseated by ranibizumab in 2006, the anti-VEGF antibody fragment derived from the full molecule bevacizumab which had been studied (and is approved) for various oncology indications. Thus was launched the “great debate” over the past five years between the two monoclonal antibodies: although bevacizumab is not approved in any ophthalmic indication, its off-label use has shown similar efficacy and safety at a substantially lower cost8,37. In early 2011, ranibizumab received EU approval for a label extension to include treatment of diabetic macular edema (DME) and regulatory submissions for the same are underway with the FDA. Lastly, the newest VEGF-inhibitor, aflibercept, which has shown similar efficacy to ranibizumab and bevacizumab in clinical trials37, was approved by the FDA in November 2011 for wet AMD; it is currently under review in the EU for AMD, and under investigation globally for DME. Regardless of their formal approvals, it should be noted that physician-prescribed use of all the VEGF inhibitors has become the standard of care for DME, retinal vein occlusion, diabetic retinopathy and other retinal disorders as well27.

Though there is room for improvement with regard to reducing the frequency, decreasing the cost12 and developing a less invasive delivery method for treating neovascular eye disease, the reality is that there are multiple viable options available for physicians and their patients. The “war” to treat these diseases is all but over, with less reason to pursue new monotherapies36.

Flying below the radar during this same period, there continues to be research for new therapies in other eye diseases. We are experiencing a resurgence in clinical stage investigation for eye diseases that currently have suboptimal standard of care. This includes, in particular, glaucoma, for which new neuroprotective agents are under investigation to complement or even replace traditional intraocular pressure (IOP) lowering therapies, and dry eye disease (DED), for which there is an improved understanding of the inflammatory nature of the syndrome. Both disorders have long had methods for treating the symptoms, but there is growing research to find therapies to resolve their underlying causes.

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Neuroprotection in Glaucoma

Glaucoma is a group of diseases resulting in damage to the optic nerve and ganglion apoptosis, which is initially manifested as visual field loss and, ultimately, irreversible blindness if left untreated1. A visual simulation of its effects is represented in Figure 1. Though typically accompanied by elevated intraocular pressure (IOP), this is merely part of the syndrome; glaucoma is more accurately described as an optic neuropathy resulting from death of retinal ganglion cells. Damage at the optic disc may result from a buildup of fluid in the anterior chamber and/or from systemic or localized hypertension. As such medicinal, laser, and surgical options (see Figure 2) typically intend to reduce IOP and thus relieve tension within the eye21.

Standard of care pharmaceutical therapies include topical eye drops which aim to increase the outflow of aqueous fluid (prostaglandins or parasympathomimetics); hyperosmotics to decrease aqueous fluid production (beta-blockers, alpha-adrenergic agonists, carbonic anhydrase inhibitors); and epinephrine which does both. Current treatments are generally insufficient in resolving the visual consequences of the actual disease13,17.

Figure 1 – A scene as viewed by someone with normal vision compared to the lost visual field effects of a person suffering from optic neuropathy related to glaucoma (courtesy National Eye Institute, National Institutes of Health).
The latest introduced therapies have targeted the reduction of dosing frequency to once or twice daily and to provide a broad array of treatment options to physicians and their patients. Laser trabeculoplasty may also be used to improve the fluid outflow through the trabecular meshwork, but multiple sessions are often required and the effect is generally limited to just a few years before retreatment or alternative therapy is sought. Conventional surgery may also be considered to physically create a new opening through which fluid may flow (see Figure 2)\(^{20}\). Alternatively, laser trabeculoplasty may also be used to provide a broad array of treatment options to physicians and their patients. Laser trabeculoplasty may also be used to improve the fluid outflow through the trabecular meshwork, but multiple sessions are often required and the effect is generally limited to just a few years before retreatment or alternative therapy is sought. Conventional surgery may also be considered to physically create a new opening through which fluid may flow (see Figure 2)\(^{20}\).

Figure 2 - Surgical methods to relieve hypertensive IOP include creation of a physical opening at the meshwork to promote fluid egress (courtesy National Eye Institute, National Institutes of Health).

Anti-hypertensives may be utilised to control blood pressure which may also have effects at the optic disc.

More recently there has been increasing evidence of the ability to treat the actual optic nerve that is damaged as a result of glaucoma with various neuroprotective agents including phenytoin, brimonidine, epigallocatechingallate, ciliary neurotrophic factor and other proprietary formulations. This is of keen interest because there currently is no way to improve vision for those patients who have irreversible impairment as a result of long-term and/or significant ocular hypertension.

Neuroprotection – the term for nervous system mechanisms protecting neurons from apoptosis\(^{34}\) – for glaucoma patients is not a new concept; published articles dating to the 1990s first introduced its viability\(^{31,35}\). However, the concept that has continued as a controversial pipe dream for the past ten years is now gaining momentum\(^1\) and advancing to the clinic. With current understanding that IOP-lowering by itself may not retard disease progression, there is significant interest in new modalities for treating glaucoma\(^{26}\). In fact, VEGF agents like those developed for age related macular degeneration and these toxic feedback mechanisms, or more directly by boosting the body’s own immunologic abilities. Neuroprotective agents have long been under investigation for other central nervous system disorders including stroke, spinal cord injuries, Parkinson’s disease and Alzheimer’s disease, and these concepts are now trickling down into eye disease research\(^{18}\). With advancements in representative animal models to improve our understanding of the biochemical pathways affiliated with glaucoma, there is a growing body of laboratory and preclinical evidence for neurological targets to include glutamate receptors, autimmune elements, neurotrophin deprivation, nitric oxide synthesis, oxidative stress products, sodium and calcium channels, heat shock proteins and apoptotic pathways\(^{2,29}\). Most human research, including the use of ciliary neurotrophic factor, brimonidine and siRNA technologies, is at the early stage in the clinic, often via investigator-led research, yet this has the potential to be an expanding field in the coming decade\(^{16}\).

Dry Eye Disease Developments

Keratoconjunctivitis sicca (KCS) or dry eye disease (DED) is a multifactorial disorder of the tears and the ocular surface that results in symptoms including discomfort (burning, itching, pain), visual disturbance, foreign body sensation, light sensitivity (photophobia), and tear film instability with potential damage to the ocular surface\(^{19}\). Aqueous tear deficiency (ATD) is the most common cause of DED impacting the tear layer which covers the normal ocular surface and serves as a surfactant, as an aqueous barrier to retard evaporation, and provides a smooth optical surface.

DED is a common disorder whose prevalence increases with age and has been estimated to affect up to 10% of non-contact wearers and up to 50% of those who wear contact lenses\(^\). DED can be classified as Sjögren’s syndrome-related versus other causes. DED also particularly affects postmenopausal\(^{11}\) or pregnant women and females taking oral contraceptives or hormone replacement therapy (especially estrogen-only pills). Also, certain systemic medications, such as antihistamines or beta-blockers, tend to decrease tear production leading to dry eye syndromes. Incidence among industrialised countries is comparable.

Dry eye is diagnosed via a combination of patient history and various tests, but no single assessment permits absolute diagnosis. Since DED is recently associated with structural or functional changes resulting from inflammation\(^{10,13}\), the use of topical steroids or non-steroidal anti-inflammatory medications may be prescribed, and topical antibiotics may be necessary if the dry eye syndrome is associated with corneal complications; however, to date, approved therapies have been primarily limited to artificial lubricants with no impact on the underlying causes of DED, and, in more severe cases, topical immunomodulating therapy (cyclosporine). Restasis cyclosporine ophthalmic emulsion remains the only approved prescription pharmaceutical specifically labelled for DED, and it is only approved in the US with moderate improvement for tested research subjects. Not surprisingly, greater than 90 per cent of ophthalmologists indicate more and better treatment options are needed for DED\(^3\).

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With limitations in the efficacy and availability of DED therapies, there is great opportunity for improvement. Further, there is a wealth of recently developed knowledge about the underlying etiology of DED, including aspects of tear evaporation, insufficient tear production, tear film instability and the inflammatory basis for the disease allowing development of new pharmaceutical targets. In addition, we are witnessing a growing wave of clinical investigative programmes targeting new methodologies of treating DED, including topical and oral anti-inflammatory combinations, adjuvant therapies to and/or improved formulations of cyclosporine, and other novel approaches. A selection of leading clinical candidates summarised in Table 1 demonstrates over a dozen programmes that are in or approaching late-stage research.

Glaucoma and DED Clinical Research in Emerging Markets

Like many therapeutic areas, clinical research in eye diseases has frequently been limited primarily to North America and Western Europe. Historically, countries in these regions have trained physicians, educated and motivated patient populations and a clinical research support network to conduct eye disease trials. These countries are also utilised with consideration for the clear regulatory paths to marketing approvals with infrastructure readily in place for future sales distribution. Even today there remains an imbalance; a review of all active studies in glaucoma and DED reveals there are more ongoing trials in the US and Canada than all other countries combined, as demonstrated in Table 2.

Table 1 – Select clinic-stage investigational products for dry eye disease.

<table>
<thead>
<tr>
<th>Sponsor Company</th>
<th>Investigational Product</th>
<th>Development Status</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcon Vision</td>
<td>XVE-1119 (reinax)</td>
<td>Phase II</td>
<td>Topical and inhaled anti-inflammatory for ocular use</td>
</tr>
<tr>
<td>Exptide Pharmaceuticals, Inc.</td>
<td>EGP-437 with EyeGadget II System</td>
<td>Completed Phase III</td>
<td>Topical anti-inflammatory for treatment of dry eye syndrome</td>
</tr>
<tr>
<td>Latte Sciences (license for ophthalmic indications from XiFab Life Sci.)</td>
<td>LXX14 (vaccinoposin)</td>
<td>Completed Phase I</td>
<td>Nanomicro-emulsified delivery of ocular anti-inflammatory therapy</td>
</tr>
<tr>
<td>Naturex Pharmaceuticals</td>
<td>MM-03</td>
<td>Completed Phase II</td>
<td>A small molecule tyrosine kinase receptor agent that inhibits mast cell degranulation and decreases ocular inflammatory properties</td>
</tr>
<tr>
<td>Novartis Pharmaceuticals</td>
<td>NAB101</td>
<td>Enrolling Phase I</td>
<td>Humanized monoclonal antibodies that block inflammatory properties of TNF-α</td>
</tr>
<tr>
<td>OphthalMed Inc. (previously Serenis Corentis Management, Inc. and the Ciba-Corning Diagnostics)</td>
<td>OF-501</td>
<td>Enrolling Phase I</td>
<td>Orally administered anti-inflammatory small molecule</td>
</tr>
<tr>
<td>Ocumax Pharmaceuticals Ltd. and Aspectus Inc.</td>
<td>Remaplitin ophthalmic suspension</td>
<td>Completed Phase II</td>
<td>Topical micro-emulsion that reduces inflammation</td>
</tr>
<tr>
<td>Regenerix BioPharmaceuticals, Inc.</td>
<td>RGN-259 (rhynosec beta 4)</td>
<td>Completed Phase I</td>
<td>Topical micro-emulsion that reduces inflammation</td>
</tr>
<tr>
<td>Neovis Pharmaceuticals</td>
<td>RX-10046</td>
<td>Completed Phase II</td>
<td>A synthetic retinal pigment epithelium-specific anti-inflammatory</td>
</tr>
<tr>
<td>Istituto Farmaceutico Co., Inc.</td>
<td>BE-110</td>
<td>Completed Phase II</td>
<td>A systemic glucocorticoid glucocorticoid receptor agonist (LRGR)</td>
</tr>
<tr>
<td>OphthoRx Biocare, Inc.</td>
<td>SAR-1118</td>
<td>Enrolling Phase II</td>
<td>A selective glucocorticoid receptor agonist (LRGR)</td>
</tr>
</tbody>
</table>

Table 2 – Number of recruiting trials (courtesy ClinicalTrials.gov on 24 January 2012).

<table>
<thead>
<tr>
<th>Region</th>
<th>DED Recruiting</th>
<th>Glaucoma Recruiting</th>
</tr>
</thead>
<tbody>
<tr>
<td>North America</td>
<td>31</td>
<td>91</td>
</tr>
<tr>
<td>Europe</td>
<td>9</td>
<td>34</td>
</tr>
<tr>
<td>Asia-Pacific</td>
<td>7</td>
<td>27</td>
</tr>
<tr>
<td>Middle East</td>
<td>14</td>
<td>16</td>
</tr>
<tr>
<td>South America</td>
<td>2</td>
<td>5</td>
</tr>
</tbody>
</table>

Though there is no shortage of interested ophthalmologists or patients in the US, Canada and Western Europe, clearly the clinical research space is far more saturated in these locations. Ophthalmic investigative sites in these regions are frequently saddled with multiple ongoing studies across all indications, even concurrently running studies that may compete for the same patient enrolment, with study coordinators dividing their attentions across many protocols. Thus, there is growing commercial interest in conducting eye disease research in emerging territories. Considering the current challenges of the global economic downturn, there are great financial incentives to conduct a higher proportion of research in markets where financial hurdles may be lower.

For glaucoma, much of the neuroprotective research is still in preclinical stages. Thus, there are significant opportunities for investigator-led research which may be initiated from any location in order to discover or advance early therapeutic candidates. As expansion to human trials continues, there is need for more comprehensive multidisciplinary sites than what has been required for glaucoma studies historically. This is because new investigational therapies may require intravitreal injections typically performed by retinal specialists, or intravenous delivery, collaboration with other sub-specialists such as ocular immunologists and advanced diagnostics such as optical coherence tomography (OCT), confocal scanning laser tomography (CSLT), scanning laser polarimetry (SLP) and photographic imaging of the optic nerve head (ONH) for visualisation of damage and treatment effects at the back of the eye (9). Clinical sites who have been certified in protocol-conduct of diagnostic imaging and ETDRS best-corrected visual acuity assessments will have a "leg-up" at the feasibility assessment stage for new trials. As these technologies, training and expertise continue to expand to emerging markets, there will be greater interest to place industry-sponsored studies in locations that are less commonly used today.

For dry eye studies, the "barriers" to participation are typically low. Patients are frequently diagnosed and treated by general ophthalmologists, low-tech diagnostics are commonly employed, and procedures are generally non-invasive. And, with an aging global population over the next two decades, there will be a ready and growing patient pool for participation in DED clinical research; this is well-timed with the advancement in therapies as discussed previously. One technique that potential sites may consider performing regularly is measurement of tear osmolarity, as this has not been standard practice for DED in the past, but is expected to be a more frequently used assessment in future research.
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With the frequency and clinical diagnosis of DED higher in the Hispanic and Asian populations than in the Caucasian population, emerging markets are ideally suited for conduct of research studies for new DED therapies.

References