ELSEVIER

Every day 100 people in the UK start to lose their sight

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New therapies to treat sight loss in an ageing population

An ageing population

The UK population has aged considerably in the past 50 years. The number of people over 60 has increased from 16 to 21% and is projected to increase to 24.2% by 2020. Similar increasing trends are projected worldwide [1]. The ageing of the world's population reflects significant advances in medicine, nutrition and technology. However, this positive development also means that an increased number of people will be affected by the adverse effects of ageing as well as from age-associated diseases.

Ageing predisposes us to conditions affecting virtually every part of the body and this is especially true for our eyes and ears. In this special issue of *Drug Discovery Today*, produced in conjunction with Fight for Sight (see Box 1) and the RNID, Goldman and Holme in their editorial address the impact of hearing loss and tinnitus in an ageing population and look at current research in this field. Sight, the sense that 9 out of 10 people most fear losing, is severely affected by age. In the UK it is estimated that 28% of people aged 65+ have difficulties with their eyesight. Losing sight does not just affect the eyes but impacts all aspects of life from practicalities to social relationships resulting in a significantly reduced quality of life for those affected. This editorial highlights recent advances in the treatment of vision impairment and blindness in an ageing population.

The ageing eye

Worldwide there are 314 million people blind or visually impaired. It is estimated that in the UK there are between 1.6 million and 2.2 million people aged 65 and over with visual acuity ranging from mild to serious levels of visual impairment [2]. In the US, more than 38 million people aged 40 and older are blind or visually impaired, or have an age-related eye disease [3,4]. There are four major age-related eye diseases that rob the elderly of their sight: age-related macular degeneration (AMD), diabetic retinopathy, glaucoma and cataract.

AMD is the leading cause of blindness in people over 60 in the developed world. An estimated 1.8 million age 40 and older in the US have advanced AMD with another 7.3 million at a substantial risk of vision loss from AMD [3,5]. In the UK it has been estimated that there are at least 500,000 people affected by AMD but a recent study has put this figure much higher [6]. In England and Wales, the most commonly recorded main cause of certifications for blindness in people aged 65 and above is AMD with glaucoma and diabetic retinopathy as the next most commonly recorded main causes [7]. In the next decade the prevalence of vision loss in the UK adult population as a result of AMD is predicted to rise by 31%, cataract by 20%, diabetic retinopathy by 16% and glaucoma by 25% [6].

Apart from the health and social impacts resulting from sight loss, there are also significant economic impacts. Looking at direct

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BOX 1

About Fight for Sight

Fight for Sight is the UK's leading charity dedicated to funding world-class research into the prevention and treatment of blindness and eye disease. Our current research programme of over £5 million is supporting research at major centres of excellence with a key focus on preventing and treating age-related eye conditions. Our current research includes:

- **Age-related macular degeneration**: investigating ways of preventing and delaying the onset of disease using laser therapy, identifying new therapeutic targets, as well as stem cell transplantation to repair the damaged retina. Research is also underway to help maximise peripheral vision in those affected by AMD.
- **Diabetic retinopathy**: studying how diabetes disrupts control of retinal blood flow and the potential therapeutic role of VEGF isoforms and identification of new drug targets. Mapping the global burden and assessing the visual disability associated with the disease is also ongoing.
- **Glaucoma**: identifying the underlying causes of glaucoma and the development of novel stem cell therapies to regenerate and repair the damaged optic nerve, as well as investigating new drug targets.
- **Cataract**: studying the molecular events leading to cataract and 'after cataract' formation, as well as identifying the genetic causes.

Fight for Sight also funds research into the prevention and treatment of childhood blindness and a large number of rare eye diseases.
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costs to the health-care system and indirect costs, such as unemployment, the total economic cost of adult sight problems in the UK in 2008 was £6.5 billion and is expected to rise to £7.4 billion by 2013 [6]. The annual cost of adult vision loss in the US comes to more than $51 billion—a huge share of the $68 billion annual cost of all vision impairment and eye disease.

New therapies for old eyes

The discovery of vascular endothelial growth factor (VEGF) and its role in wet AMD and diabetic retinopathy has triggered a surge of interest in anti VEGF therapies that has translated into benefits for those affected. Anti-angiogenic therapies – pegaptanib (Macugen; Pfizer) and ranibizumab (Lucentis; Novartis) – have markedly improved outcomes for patients with wet AMD, showing stabilisation of vision and frequent improvements in visual function. However, shortcomings of the current drugs such as short half-life, intraocular dosing, limited effectiveness in some patients, and potential systemic side effects continue to drive the development of new agents. As reviewed by Anderson *et al.*, in this issue of *Drug Discovery Today* research is continuing to find the optimum therapeutic approach, better delivery of drugs to the retina in a safe and cost-effective manner. Research also continues to unveil many other interesting avenues for potential intervention. Combining different strategies targeting angiogenesis, inflammation and apoptosis, or treating at an early stage or even prior to the formation of choroidal neovascularisation with kinase inhibitors, may improve the future management of AMD. In addition, use of combination therapies such as verteporfin photodynamic therapy and epiretinal brachytherapy (radiation) to complement VEGF inhibition are in clinical trials (see: http://clinicaltrials.gov/). The first trials to test the efficacy of Ellex 2RT, a novel laser therapy to 'clean up' Bruch's membrane are planned. This therapy has the potential to change the way patients with both wet and dry AMD and diabetic retinopathy are treated because it targets the disease in its early stages before vision is lost (see: http://www.ellex.com.au/).

The dry form of AMD, which leads to a slower, but significant loss of vision, still represents a major challenge with no treatment currently available. Research has focused on accumulation with age of toxic by-products of the visual cycle in the retinal pigment epithelium (RPE), drusen formation, complement activation, and nutritional risk factors as well as predictive clinical biomarkers in dry AMD. Based on these developments, therapeutic targets have been identified and many drugs are now in clinical trials and are showing promising results. Positive interim data results from the Phase II trial of OT-551, an eye drop that targets oxidative stress and inflammation pathways, has been announced by Othera Pharmaceuticals Inc. The 12-month findings from the two-year OMEGA trial are reported to show an emerging trend for a moderate reduction in vision loss in patients with dry AMD who were treated with OT-551. Another compound ACU-4429 (Acucela), an orally administered non-retinoid visual cycle inhibitor molecule, has also shown promising results in a Phase II trial in patients with dry AMD.

Stem cell therapy offers real promise for the treatment of both wet and dry AMD and is now beginning to move from the lab into the clinic. The recent Pfizer/University College London collaboration brings together the pioneering work of university researchers in the field of cell-based therapies and Pfizer's expertise in the design and delivery of therapeutics. The collaboration will advance the development of human embryonic stem cell (hESCs)-derived retinal pigment epithelium as a therapy for AMD with clinical trials planned for early next year. In the US, Advanced Cell Technology in collaboration with researchers at the Casey Eye Institute, Oregon, are also validating the stem cell technology platform for the treatment of retinal disease. The first trial of its RPE cell programme for the treatment of Stargardt's macular dystrophy, the most common cause of juvenile macular blindness, could start as early as this year if the Food and Drug Administration (FDA) gives approval. The first clinical trial for a therapy generated by hESCs was approved last year by the FDA for spinal cord injury and this has paved the way for further trials in other disease areas.

Induced pluripotent stem cells, made by genetically manipulating adult skin cells to give them the versatile properties of hESCs are being explored as possible therapies for diseases and are providing a good research tool for disease modeling and drug screening. Blood and bone marrow-derived progenitor cells of patients are also being used to develop treatments for AMD. Preclinical data demonstrates that specific populations of cells may be therapeutically useful for the treatment of AMD since they target sites of neovascularisation and retinal ischaemia where they stabilize the vasculature [8].

This translation of stem cells into a medical therapy for AMD is still in its infancy and many hurdles need to be overcome. None-

theless stem cells offer great hope for its treatment and for many other retinal degenerative diseases and may indeed be a cure rather than a treatment. Ahmat *et al.*, in this issue have shown that several new surgical approaches based on transplantation of *ex vivo* expanded limbal epithelial stem cells for ocular surface disease and they discuss alternative sources of stem cells for clinical application.

Diabetic retinopathy

Diabetic retinopathy is a common complication of diabetes and has now become one of the leading causes of blindness in the working population in many developed countries and an increasingly frequent cause of blindness in developing countries. In England and Wales it is the most common cause of blindness among people of working age (16–64 years), and accounts for 15% of all blind certifications in those aged 65–74 years [7]. Diabetic retinopathy affects over 4.4 million Americans. By the year 2050 the number of people in the US over the age of 65 with diabetic retinopathy is projected to quadruple from 2.5 million to 9.9 million [3,9]. In addition to diabetic retinopathy, diabetics are also at higher risk of glaucoma, cataract, macular oedema and retinal detachment.

Diabetic retinopathy can progress from mild non-proliferative diabetic retinopathy to advanced proliferative diabetic retinopathy. Diabetic macular oedema is now the principal cause of vision loss in diabetes and involves leakage from a disrupted blood–retinal barrier. Laser surgery is usually the treatment of choice as it prevents the growth of new blood vessels and seals the fragile ones. Vitrectomy is used when there is a vitreous haemorrhage. Emerging therapies for diabetic retinopathy includes inhibition of aldose reductase/polyol pathway, non-enzymatic glycation/advanced glycation end products inhibitors, protein kinase C inhibitors, and reduction of oxidative stress/superoxide induced damage, extracellular matrix modifiers including corticosteroids, and vitreous modifiers. Newer drugs modulating growth factor and cytokine production (including VEGF, TNF and cytokines such as NF-kB) and newer targeted therapeutics utilising antisense oligonucleotides, and small interfering RNAs are also currently in clinical trials [10]. It is hoped that newer treatments, possibly used in combination with standard therapy, will offer the hope of effective and safe treatment that may allow us to improve visual outcomes and prevent the damaging consequences of diabetic retinopathy.

Glaucoma

It is estimated there are 67 million people worldwide are affected, but over 50% of these are undiagnosed. In the US 2.3 million have been diagnosed with the disease and this is projected to increase to 3 million by 2020 [3]. In the UK, around 500,000 people are affected and half of these are not receiving treatment because they are unaware they have the disease. In England and Wales glaucoma accounts for around 12% of blind certifications for those aged 65 and above [7].

Primary open-angle glaucoma, the commonest form of glaucoma, is defined as a progressive optic neuropathy with visual loss potentially leading to blindness. Several risk factors are known including increased intraocular pressure. One important way of reducing burden of disease is the development of new and safer surgical options. Research is continuing into affordable treatment options that do not require as much patient compliance and the creation of effective screening techniques to help prevent glaucoma damage through early identification of those with the disease. The current and future treatment strategies being developed for this disease are described by Dr Dahlmann-Noor *et al.*, in this issue. Among the approaches being studied are gene therapy with neurotrophic factors to promote survival of the retinal ganglion cells and stem cell therapy to regenerate the optic nerve.

Cataract

Cataract affects over 22 million Americans age 40 and older [3]. By age 80, more than half of all Americans have cataract. Cataract surgery is now the most common surgical procedure undertaken in the UK with around 300,000 operations per year in England alone. With the increasing life expectancy and an expanding elderly population, the incidence of cataract and therefore of surgery continues to rise. Although cataracts are not preventable, their surgical treatment is one of the most cost-effective interventions in healthcare. Ongoing research into the normal healthy functioning of the eye's lens may help us better understand the causes of cataract and how they might be prevented.

Hope for the future

Advances in our understanding of the pathogenesis of eye disease are key to the development of new therapies. Current vision research, in the UK at least, is largely independent researcher lead and these approaches have been highly successful in providing critical breakthroughs that have increased our understanding of the disease process. Newer therapies based on this knowledge are being developed especially for diseases such as AMD, glaucoma and diabetic retinopathy. However the translation into clinical benefits for our elderly population who have low vision or are blind can be considered slow especially for AMD. Many opportunities exist to prevent vision loss and restore vision for the millions of elderly people affected but funding in this area is pivotal.

In the UK, the Medical Research Council (MRC) and the Wellcome Trust (WT) awarded £9.7 million and £10.7 million, respectively, towards vision research representing ~2% of their overall research budgets for 2007/2008 (information obtained directly from the MRC and the WT). Fight for Sight, the UK's largest charity dedicated to funding vision research has an ongoing commitment of over £5 million for research into the prevention and treatment of blindness and eye disease, as well as investigating ways to improve functional vision in those affected by AMD. Fortunately, vision research is resulting in new tests and imaging technologies to diagnose eye disease, as well as treatments and therapies that not only stabilise but also restore vision loss. With innovation in vision research bringing hope for major advances and breakthroughs, it is critical to ensure that research and incentives for innovation continue to be funded. The increased healthcare spending on eye-related diseases in the developed world is creating a strong demand for newer more effective treatments that in turn is leading to a rise in investment in ophthalmic drug research. The future looks bright as 65 of the 2000 medicines for the elderly currently being tested in clinical trials or awaiting FDA approval, are medicines in development for the treatment of eye disease targeting AMD, diabetic retinopathy and glaucoma [11].

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