Eye research: where next?

BY ROD MCNEIL

Eye research in the UK is underfunded relative to other areas of medical research and general awareness of sight loss and its prevention remains poor, messages that were reinforced in presentations and discussions during a recent research summit meeting in London hosted by the eye research charity Fight For Sight and Vision UK. So where next for eye research?

One patient with retinitis pigmentosa who participated in the very first gene therapy trial for hereditary retinal disease spoke about his experience. He was asked what mattered most to him from ongoing and future medical research in the ophthalmology field. He said it was a question of giving an individual some hope and optimism about the future. The biggest challenge, he said, is not knowing when or whether vision will deteriorate further and whether this will undermine the ability to work independently.

The patient voice in ophthalmology is beginning to be recognised and can contribute to key areas, including priority setting and shaping the direction of the research agenda, communicating the wide-ranging impact of disease and identifying outcome measures that matter most to those affected by visual impairment [1].

In a number of eye conditions, there can be wide-ranging systemic, psychological, emotional and social effects of both the disease and its treatment. As noted by Dean et al., objective clinical measures such as visual acuity, while important, do not alone provide an adequate assessment of the overall impact of ophthalmic disease on a patient's functional vision or daily life [1]. This can lead to a discordance between patient priorities and perspectives and the efforts of clinicians and other stakeholders. Learning to hear the 'patient voice' is central to realigning the care and research agenda according to patient priorities [1].

Delivering solutions that patients want

Fight for Sight currently spends over £3 million a year funding pioneering and vital sight loss research, ahead of Moorfields Eye Charity (£2.2m) and the Macular Society (£0.6m). Its current overall research commitments are 159 projects at 44 different universities and hospitals.

Total expenditure on medical research by Association of Medical Research Charities (AMRC) members was £1.6 billion in England in 2015/16, while expenditure on eye research totalled £6 million (not including Wellcome Trust data), representing less than half of one percent of total medical research expenditure by UK charities. Fight for Sight and Vision UK believe that eye charities and partners need to step up the emphasis and resources given to eye research.

Vision UK is the independent partnership organisation that aims to mobilise the eye health and sight loss pathway for the benefit of blind and partially sighted people, their communities and the general population including those at risk of sight loss. The number one priority area in the Vision UK ambition statement is to improve the nation's eye health and end sight loss, and that necessitates prioritising eye research.

Commenting on next steps for Fight for Sight of interest to health professionals and research clinicians, Michele Acton, CEO of Fight for Sight, observed: "Over the last decade we have seen great progress in our understating of sight loss and we are starting to see early phase trials of potential new treatments for eye diseases and conditions that are currently untreatable.

"In 2017 Fight for Sight launched a new strategy aimed at capitalising on this progress. The new strategy has at the heart of it a focus on delivering solutions that patients want. With limited funding the new strategy targets Fight for Sight funding to research areas where the charity can have most impact and emphasises Fight for Sight's aim to work in collaboration with others in the eye health sector to address sight loss."

Globally, need for scale-up

The Global Burden of Disease study highlighted in 2016 the rising importance of chronic disability. While health is improving globally, more populations are spending more time with functional health loss. Investigators argued that country-specific drivers of disease burden should be identified so as to inform research investments, prevention efforts, health policies and health system improvement initiatives [2].

Loss of vision and age-related eye diseases are major global public health problems [3]. The economic impact of sight loss and blindness in the UK adult population totalled an estimated £28.1 billion in 2013, according to research commissioned by Royal National Institute of Blind People (RNIB) [4]. Only around a quarter of registered blind and partially sighted people of working age are in paid-or self-employment, compared with around three quarters of the UK general population [5].

The Global Vision Database (GVD), established by an international consortium of ophthalmologists and optometrists called the Vision Loss Expert Group, aims to develop and deploy new and improved evidence on the prevalence of blindness and vision impairment. As well as advising the World Health Organisation and other international organisations, the GVD provides advice to researchers and public health officials on the different issues involved in the estimation of cause-specific blindness and vision impairment.

The Vision Loss Expert Group recently published results of a systematic review and meta-analysis showing there is an ongoing reduction in the age-standardised prevalence of blindness and visual impairment [6]. However, the growth and ageing of the world's population is causing a substantial increase in the number of people affected. These findings, together with a very large contribution from

Table 1: Categories of vision impairment with corresponding visual acuity [6].

	Presenting visual acuity* in the better eye
Mild visual impairment	<6/12 but 6/18 or better
Moderate and severe visual impairment	<6/18 but 3/60 or better
Blindness	<3/60
Presbyopia	Near vision worse than N6 or N8 at 40cm and best corrected visual acuity ≥6/12 (20/40)

*Snellen visual acuity or the equivalent calculated from published logarithm of the minimum angle of resolution values.

uncorrected presbyopia, highlight the need to scale-up current vision impairment alleviation efforts at all levels to eliminate the burden of unnecessary blindness and vision impairment, noted the authors [6].

Globally, of the 7.33 billion people alive in 2015, an estimated 36 million were blind, 216.6 million people had moderate to severe visual impairment (MSVI), and 188.5 million had mild visual impairment (Table 1) [6]. The estimated number of blind people increased by 17.6%, from 30.6 million in 1990 to 36 million in 2015. The number of people with MSVI also increased (+35.4%), from 159.9 million in 1990 to 216.6 million in 2015. Preventable vision loss due to cataract and refractive error continue to cause most cases of blindness and MSVI in adults aged 50 years and older [7]. The number of blind people is projected to increase to 38.5 million by 2020 and 115 million by 2050.

UK National Eye Health Survey: addressing the UK eyecare challenge with relevant actionable data

It is estimated that the prevalence of blindness and MSVI has been reduced by 50% and 38%, respectively, from 1990 to 2010 in highly developed countries [8]. Macular degeneration has become the most important cause of blindness in high-income countries. Uncorrected refractive error, followed by cataract, macular degeneration, glaucoma and diabetic retinopathy, was the most common cause for MSVI in 1990 and 2010.

The UK currently has no nationwide population-based data on the prevalence and causes of vision impairment. This is of great concern, given that health interventions and future programs have no evidence base other than a few small local population-based studies performed 20-30 years ago, explained Professor Rupert Bourne, Vision and Eye Research Unit, Anglia Ruskin University, Cambridge, UK, speaking at the London research summit.

To address this lack of a nationally-representative dataset, the UK National Eye Health Survey (UKNEHS) will capture quality data on vision and eye health for adults across four nations, generating actionable data that may help translate research into better outcomes (Table 2). Currently it is not known if resources are best deployed, certain groups do not have parity of access to eye care and decision makers still do not understand the importance of eye health and the relationship with general health. Moreover, demand for eye care currently outstrips capacity and the full extent of demand is not known.

The UKNEHS represents a national collaboration of researchers in partnership with government, non-governmental organisations and industry that will answer questions regarding inequity of care, healthcare delivery, patient / public / carer attitudes to eye care and research implications, including ocular diseases, interaction of ocular disease with other systems, and environmental interactions. Investigators are working with the National Institute for Health Research (NIHR) to make this a 'portfolio study', involving alignment with Accelerating Digital and other programs.

The UKNEHS is an inclusive collaborative nationally relevant study, with international and national / local benefits for the population and fundamental for UK research, added Prof Bourne. There will be active involvement in UKNEHS by trainees in ophthalmology and optometry, sparking greater research awareness and capability in next generation workforce. The initiative will help also to promote UK eye research nationally and internationally. Advocacy through the UKNEHS and public campaign will further heighten awareness of eye health.

Responding to patient priorities: a call for action to discover an effective intervention to prevent progression of early AMD

The Action Against Age-Related Macular Degeneration (AAA) partnership is a new research initiative focused on how to stop early age-related macular degeneration (AMD) turning into late or advanced AMD, a

Table 2: UK National Eye Health Survey: research implications.

Addressing UK eyecare challenge		
1. Health and wellbeing gap	Radical upgrade in prevention	Incorporating: • Data analytics, machine learning, artificial intelligence • Digital and m-Health • Advanced technology • Social inclusion and networking • People centred
2. Care and quality gap	New care models	
3. Funding gap	Efficiency and investment	

Table 3: How to stop early AMD turning into late AMD? Top research priorities*.

Action against AMD: 10 priority research questions:
• Cohorts for longitudinal studies of genetically defined, highly informative subject subsets
• Ageing changes in the choroid-photoreceptor complex
• Development of models of choriocapillaris endothelium and retinal pigment epithelium (RPE) ageing
• Integrated approach to understanding how ARMS2/HTRA1 polymorphisms drive disease risk
• Understand lipid and membrane handling in the choroid-photoreceptor complex
• Approaches to revitalising Bruch's membrane
• Support for a drug development program and studies of therapeutic access to RPE-photoreceptor complex
• Understanding mechanisms of impaired dark adaptation in early AMD (both to support appreciation of how early disease develops as well as developing a potential 'marker' of early disease)
• Work with other programs to develop imaging / functional tests for early disease
• Advance understanding of how the innate immune system drives disease

*Source: How to stop early AMD turning into late AMD? Action Against Age-Related Macular Degeneration. Wellcome Genome Campus, Hinxton, Cambridge, UK; 5-6 June 2017.

shared intent of the three founding charities, Fight for Sight, the Macular Society and Blind Veterans UK. The primary objective is to act as a catalyst organisation to facilitate the funding of medical research aimed at finding an effective treatment for early-stage AMD.

While AMD is the commonest cause of visual impairment in the developed world, to date there is no intervention that slows or prevents early disease progressing to neovascularisation or geographic atrophy. The Wellcome Genome Campus Retreat entitled 'How to stop early AMD turning into late AMD?' was held in June 2017, involving a global summit of experts in different areas of both basic and clinical research on AMD.

The Wellcome-funded conference identified top research priorities designed to lead as rapidly as possible to effective treatment(s) or strategies to prevent individuals with early AMD progressing to late AMD [9]. Table 3 summarises priority research questions from this initial global forum [9]. Infrastructure priorities include seed-corn funding, followed by development of academic and commercial partnerships and non-clinical researcher capacity building. The ambitious goal is to discover and develop an effective preventive intervention for early AMD within 10 years.

The NIHR health research system

The NIHR was established by the Department of Health in 2006 to improve the health and wealth of the nation. Sine Littlewood, Head of Business Development and Marketing at the NIHR Clinical Research Network (CRN), provided an overview of the NIHR health research system (Figure 1). The NIHR funds high-quality research, provides world-class research facilities and support for research in the NHS, works with the life sciences industry, charities and public funders and involves patients and the public across all its work and enables them to participate in research.

In 2016/17, the NIHR CRN supported 2055 new studies and recruited more than 665,000 participants into clinical trials. Of these, around 15,000 participants were recruited for eye research-related studies. The NIHR has also introduced a 70-day benchmark for enrolling the first patient into a trial by participating NHS Trusts. Almost all NHS trusts (99.9%) and 48% of GP practices were research active in 2016/17.

NIHR has awarded over £4 million in funding related to Sight Loss and Vision Priority Setting Partnership priorities, e.g. binocular optical coherence tomography (OCT) and the potential to reinvent the eye examination, addressing AMD priority 6 to identify the most effective way to detect and monitor the progression of early AMD. Funded via a NIHR Clinician Scientist Award, Dr Pearse Keane and consultant colleagues at Moorfields will assess the accuracy, reliability and reproducibility of binocular OCT tests, initially on patients with AMD and diabetic retinopathy. The results of this five-year study will facilitate future plans for incorporation of binocular OCT into randomised clinical trials and the assessment of its effects on clinical outcomes.

In partnerships between England's leading NHS organisations and universities, the 20 NIHR Biomedical Research Centres provide expertise and leadership in translational research across a broad range of disease and therapy areas, including cancer, cardiovascular disease, dementia and neurodegenerative disease and eye disease. Additionally, the NIHR Innovation Observatory, involving an independent research team at Newcastle University, is focused on emerging healthcare technologies. It offers academia and industry insights to identify areas to develop that can provide better healthcare and allow an opportunity for new innovations to be used in practice more rapidly. It also advises NHS policy and decision makers (e.g. NHS England and NICE) and NIHR research programs.

As well as providing an integrated health research system, including co-funding health research, NIHR plays a major role in developing research capacity. A major focus of its capacity development work is in applied and clinical research and there are integrated training pathways with awards from other funding bodies such as the MRC and Wellcome Trust. For an update on the NIHR vision for tomorrow's health research leaders, see: https://www.nihr.ac.uk/our-faculty/documents/TCC-NIHR-Strategic-Review-of-Training-2017.pdf

Charity funding was catalyst for Nightstar formation and advancing development of gene therapy for retinal dystrophies

Nightstar Therapeutics plc is a clinical-stage gene therapy company focused on developing and commercialising novel one-time treatments for patients suffering from rare inherited retinal diseases that would otherwise progress to blindness. The Oxford spinout was floated as a public limited company in September 2017, with a NASDAQ market capitalisation exceeding $400 million at the time of flotation. Initial £300,000 seed funding from Fight for Sight was the catalyst for the company's eventual formation, illustrating the value of charity funding of early-stage eye research in basic and preclinical investigations.

The company is developing a pipeline of proprietary gene therapy product candidates that are designed to substantially modify or halt the progression of inherited retinal diseases for which there are no currently approved treatments. Its lead product candidate, NSR-REP1, for the treatment of choroideremia (CHM), is expected to enter phase 3 clinical development (STAR registration trial) in the first half of 2018 and

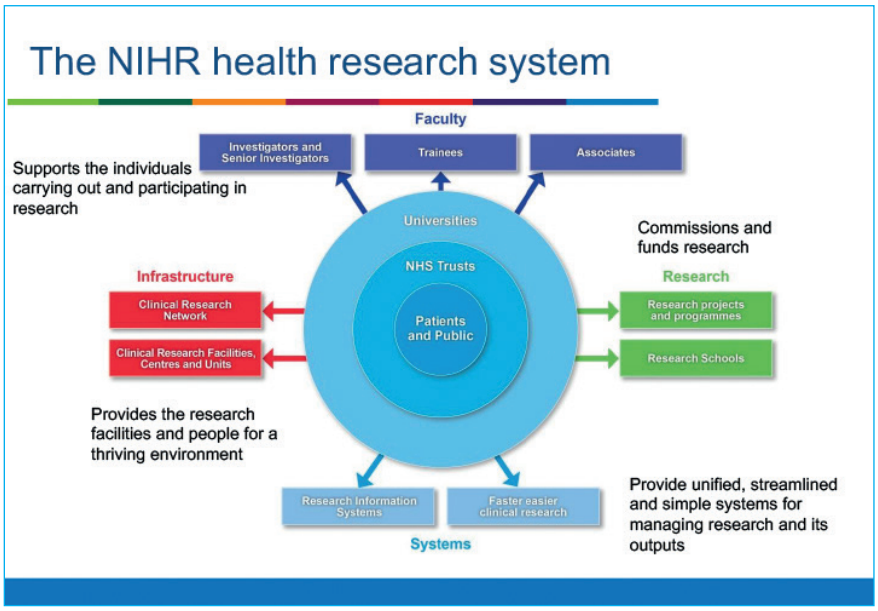

Figure 1: The NIHR health research system.

represents the most clinically advanced product candidate for this indication worldwide.

The treatment goal is to improve visual outcome by rescuing retinal cells through gene therapy. After one-year follow-up, over 90% of patients (n=31) treated with NSR-REP1 for CHM across four open-label investigator-sponsored clinical trials had either maintained (either gain or within one line of baseline) or improved visual acuity (VA) from baseline. In addition, 21% of treated patients achieved a 15-letter or greater VA gain from baseline at one year (n=19).

Professor Aniz Girach, Chief Medical Officer, Nightstar Therapeutics plc, explained that CHM is a rare, degenerative, X-linked genetic retinal disorder primarily affecting males, with no current treatments, and represents a significant unmet medical need. CHM presents in childhood as night blindness, followed by the progressive constriction of visual fields, generally leading to vision loss in mid adulthood and total blindness thereafter. Patients generally maintain good VA until the degeneration of surrounding retinal cells encroaches onto the fovea. The prevalence of CHM is estimated to be one in 50,000 people, implying a total population of approximately 13,000 patients in the United States and the five major European markets.

Nightstar is also conducting a phase 1/2 clinical trial with its second gene therapy product candidate, NSR-RPGR, for the treatment of X-linked retinitis pigmentosa (XLRP), with preliminary data expected in 2018. XLRP accounts for approximately 15% of all cases of retinitis pigmentosa, an inherited X-linked recessive retinal disease characterised by a lack of protein transport that leads to a loss of photoreceptors. Approximately 70% of XLRP cases are due to mutations in the genes for the retinitis pigmentosa GTPase regulator, or RPGR. The estimated worldwide prevalence of XLRP due to RPGR variants is approximately one in 40,000 people.

Another product candidate, NSR-BEST1, is in preclinical development for the treatment of Best vitelliform macular dystrophy. A phase 1/2 trial in patients with Best disease is expected to be initiated in 2019. The company is also evaluating additional in-licensed preclinical programs as well as other in-licensing opportunities to potentially broaden the pipeline and drive future growth. Prof Girach added that the company is focused on building strong collaboration with an established network of retinal disease centres of excellence globally, as well as long-term partnerships with patient advocacy groups worldwide such as Fight for Sight.

Eye research: learning from progress made in other health areas

What can eye charities and other funders of eye research learn from progress made in dementia and other donor-driven research areas? Engage with industry as well as other potential collaborators outside the sector. It is also important to be open and creative about what can be achieved. Top-line ambition statements need to be credible. Political support can be hugely beneficial in prioritisation of health research interests, so charities should continue to lobby the Government to pay attention, e.g., doubling the amount spent on eye research could revolutionise eye health.

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