FT Health Eyecare

Thursday October 13 2016

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Drugmakers respond to growing need for treatments

The fast rise in numbers of people going blind has prompted a revival in research, reports *David Crow*

Of the five senses, none may be more precious than sight. Yet even as other areas of medicine have advanced rapidly in recent decades, the area of eyecare has been comparatively static, especially when it comes to developing new drugs.

"Eyecare between the 1980s and early 2000s was essentially the domain of surgeons, who were eventually helped by lasers," says Dr Bernard Gilly, the chief executive of GenSight Biologics, a Paris-based company developing gene therapies for eye diseases.

In recent years, eyecare research has had something of a renaissance, however, thanks to the combination of escalating need for treatments and some important scientific discoveries.

By 2050, the number of people with visual impairment or blindness is set to double to more than 8m in the US alone, according to official figures. "Novel approaches are being tested across all the major ophthalmology conditions," notes Dominic Trewartha, an analyst at healthcare investment specialist GBI Research. He estimates that pharmaceutical companies are developing almost 160 first-of-a-kind drugs to treat everything from diseases associated with ageing, such as macular degeneration and glaucoma, to rare genetic conditions that cause blindness in younger people.

The runaway success of two drugs that treat a form of age-related macular degeneration, known as wet AMD, has lifted drugmakers' spirits. Lucentis, sold in a partnership between Swiss pharma groups Novartis and Roche, generates billions of dollars in annual sales, as does Eylea, which was discovered by New York-based biotech Regeneron.

"The very big success of these two drugs has clearly pulled the domain of eyecare to the forefront," says Dr Gilly.

Testing times: eyecare has emerged from a relatively static period — Getty Images

Several conditions still have no treatment, such as dry AMD. Roche is testing one potential treatment, Lampalizumab, in late-stage clinical trials. Nonetheless, Umer Raffat, analyst at investment banking services adviser Evercore ISI, says: "We're hearing a lot more about eyecare recently, much more than we did, say, two or three years ago."

He points to the approval of a new drug for dry eyes, Xiidra, made by Shire, the Anglo-Irish drugmaker, which is expected to become a blockbuster medicine, defined as one with sales of a billion dollars a year and more.

The rise in activity has led to more dealmaking in eyecare. The past decade has brought $20.9bn of licensing deals, where larger pharma groups buy the rights to drugs developed by smaller companies. There have been a further $12.9bn of development agreements, where drugmakers pursue a new medicine in partnership, says GBI Research.

Among the most active companies has been Allergan, the maker of wrinkle smoothener Botox, which has one of the world's biggest eyecare franchises. In August, the company bought ForSight, which makes a so-called periocular ring — a device that rests on the eye under the lids. The hope is to use it to administer Lumigan, a glaucoma treatment at present available as an eyedrop.

Such a device could help combat poor adherence — patients not taking their medication regularly enough — which is a big obstacle to tackling glaucoma. The majority of patients are elderly and many forget to use their eye drops. Glaucoma is expected to affect more than 80m people worldwide by 2020 and has the potential to become one of the leading causes of blindness. It might also help Allergan protect its revenues earned from Lumigan, which is anticipated to lose patent protection in the next decade.

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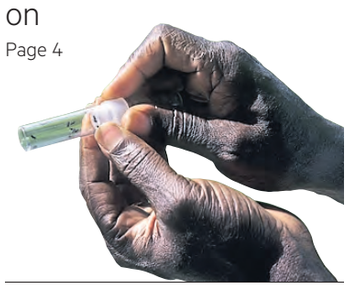


Ophthalmology closes in on the blockbusters

Pharmaceuticals
As people live longer, big companies are looking to increasingly lucrative returns, writes *David Crow*

Light sensitive: goggles can simulate the effect of AMD, a condition that is becoming far more widespread
John Birdsall/Alamy

Most blockbuster medicines, that is to say drugs with sales of $1bn and more a year, fall into three categories: anti-inflammatory wonder drugs that treat everything from arthritis to psoriasis, cancer therapies and treatments for diabetes. A fourth is becoming increasingly important to "big pharma" — ophthalmology or, more simply, eyecare.

Few illnesses correlate more closely with an ageing population than eye diseases. By 2022, the world's fifth best-selling drug with $7.7bn in annual revenues is expected to be Eylea, made by Regeneron, the large New York biotech group, says a recent report from research group Evaluatepharma. Eylea is used to treat one of the most common eye conditions, known as wet AMD that, with age, causes a breakdown of the macula, a small area of light-sensitive tissue at the back of the retina.

Left untreated, wet AMD can lead to a permanent loss of central vision. It affects about 4 per cent of white adults over 75, rising to 14 per cent for those of 80 and over. It is less common in black, Hispanic and Asian people.

The number of patients with AMD is set to rise steeply over the next few decades as people live longer, says the US National Eye Institute. It forecasts that by 2050, the number of Americans with the condition will have risen from about 2m in 2010 to almost 5.5m.

As with many new drugs, Eylea is administered by injection. Regeneron has been able to steal market share with the product because it needs to be injected only every eight weeks. This compares with four for Lucentis, which is sold in a partnership between Swiss pharma groups Novartis and Roche.

Allergan, one of the biggest players in eyecare, is developing Abicipar, now in the final stages of clinical testing and with blockbuster sales potential, analysts say. It might be administered as infrequently as every three months. "If you're going to be poked in the eye, it's quite an advantage," says David Nicholson, Allergan's head of R&D.

When late-stage trials of Abicipar began in 2014, Allergan looked to the global AMD market being about $10bn by 2019. That was predicated on high prices: Eylea costs about $1,800 per injection and Lucentis $2,000. It is unclear whether cash-strapped healthcare systems will pay for such costly drugs, especially when other, less expensive alternatives are at hand. Avastin, a cancer chemotherapy made by Roche, can be used to treat wet AMD. Since it is priced to be used in large tumour-killing quantities — and only tiny amounts need to be injected into the eye — it costs just $50 per average treatment every four weeks, says the American Academy of Ophthalmology.

The UK is debating whether doctors should routinely use Avastin "off label", that is to say deploying the drug to treat wet AMD even though it has never been tested or approved for the condition. The UK's Royal College of Ophthalmologists says switching from Lucentis or Eylea to off-label Avastin would save the National Health Service £100m a year.

> Diseases of the eye correlate closely with an ageing population

Allergan is best-known for its wrinkle smoothing treatment Botox but its next top seller is Restasis for dry eyes. Restasis generated $1bn in sales last year.

It too faces competition from Shire, the Anglo-Irish drugmaker which in July won regulatory approval for Xiidra. Unlike Restasis, Xiidra is intended not just for patients who are suffering symptoms of dry eye, such as difficulty producing tears, but also for those with signs of the condition — meaning they do not realise they have it but are diagnosed after being examined by a doctor.

Shire reckons some 16m Americans display either symptoms or signs of dry eye and analysts expect Xiidra to become a blockbuster, in part by stealing share from Allergan. Andrew Baum, an analyst at Citi, forecasts peak annual sales of $2.5bn by 2030.

The biggest threat to established ophthalmology companies may come from smaller companies *(see article down page)*. New York biotech group Ophthotech is developing the drug Fovista for AMD, which has been shown to provide a significant improvement in vision when added to Lucentis. Analysts at investment bank Leerink say the drug has huge potential to become a "foundation therapy" for AMD sufferers. Recognising the threat, Novartis and Roche have jointly secured rights to sales outside the US in a deal worth up to $1bn.

New companies such as Spark Therapeutics are investigating gene therapies to stave off blindness. Such smaller groups could win a big slice of the eyecare market, which is set to grow by 10 per cent a year from $13.7bn today to $26bn by 2022, says GBI Research.

Doors of perception remain concealed in brain of beholder

Science

Neurologists scratch their heads on how we convert the data deluge from our eyes, writes *Denis Schluppeck*

The eye: a most complex organ

Although our understanding of the nature of sight is advancing, some big mysteries still need to be unravelled. Recognising everyday objects such as chairs and tables is child's play for humans. Computer vision experts, meanwhile, struggle to build machines with the same abilities.

While the function of the eye — among the body's most complex organs — is to supply data on the visual environment to the brain, the capture of light and its conversion into electrical signals is just the first step in a long sequence of computations that results in our seeing colour or recognising faces.

The interpretation of the eye's "data stream" occurs in the intricate circuitry of the brain. At a broad level, this circuitry is quite well understood. The brain is subdivided into distinct lobes. The occipital lobe (one of four in the primate brain) and a substantial part of the temporal lobe serve vision. These are tiled with more than 30 smaller brain areas, each of which is thought to contribute a distinct set of computations that transform information for the next stage of processing.

A recent study based on data from the Human Connectome Project has provided a map of these areas in exquisite detail that goes beyond just the brain's visual areas.

At a smaller scale, though, much less is known about the computations in the networks of neurons that ultimately cause our sensations.

This is partly because the problem the brain needs to solve is ill-defined. The data coming to it from the eyes are limited by the biological process that converts light into electrical signals. Humans can only, for instance, make use of light in a relatively limited part of the spectrum.

Eyes-to-brain data are also ambiguous, since many different states of the world can give rise to the same sensory information. For example, the eyes can capture only two-dimensional representations of the 3D world.

Large numbers of scientists and a great diversity of approaches are engaged in solving the puzzle of how the brain converts the deluge of data arriving from our eyes into a sense of sight. The annual meeting of the US Society for Neuroscience, for example, attracts some 30,000 attendees.

The toolkit available to neuroscientists — to address questions from the molecular level up to the behaviour of circuits of brain cells, and even the whole organism — is rapidly expanding.

At the microscopic scale, the recent development of optogenetics has enabled scientists to control the activity of individual neurons by shining light directly on to them, in effect providing an experimental on-off switch. This allows researchers to silence specific neuron populations in order to understand their role in shaping sensation and perception.

The potential of the technique to transform neuroscience has been recognised by — among others — the award of the prestigious Brain Prize for outstanding research by neuroscientists by the Danish industrial foundation, Lundbeckfonden.

These tools are both useful for understanding the functioning of healthy visual systems and in detecting what is disrupted after trauma or stroke, cases of neurodegenerative disease, or by abnormal development.

A hugely versatile set of techniques based on magnetic resonance imaging (MRI) allows scientists to measure the anatomy and function and even localised chemical changes in brain tissue. This has enabled them to tackle questions at the macroscopic scale, namely where objects are visible with the naked eye. To track tiny electromagnetic changes outside the skull caused by the activity of neurons with millisecond accuracy, scientists can now use magnetoencephalography, or MEG.

Such techniques permit a "look inside" the human brain while participants perform various cognitive tasks. By picking the right set of experimental questions, neuroscientists hope to put together the puzzle one piece at a time.

Windows to the soul shed light on our broader state of health

Diagnostics

Regular screening has an important part to play as a tool in preventive care, reports *Sarah Murray*

Eyes may well be windows to the soul, though it turns out that they tell us plenty about our bodies, too.

The eye affords early indications of the onset of conditions such as diabetes and cardiovascular disease. Some experts argue for more regular eye examinations as a tool in preventive healthcare.

The advantage of the eye in diagnosing disease is, simply, that it is open to view. Assessing blood vessels or nerve fibres elsewhere in the body would require an invasive procedure.

"There are very few places where you can directly observe blood vessels because we're covered in a skin," says Christopher Owen, professor of epidemiology at the Population Health Research Institute at St George's, University of London. "You can do it in the fingernails but it's not as easy as taking a picture of the back of the eye."

The technology is rapidly improving. For example, digital retinal cameras developed by Japanese company Canon, that eliminate the need for bright lights and dilating eye drops, have increased in sensor resolution from 3 megapixels in 2003 to 20 megapixels today. "That allows the doctor to zoom up on that image," says Tom Russo, regional sales manager in Canon's US healthcare division.

Canon has developed software filters that clean up the retinal images of cataract sufferers and elderly people whose eye lenses commonly become yellower as they age. "The technology has evolved for decades and it's only going to get better," says Mr Russo.

Being able to obtain clear and detailed images of blood vessels or nerve fibres creates the potential for faster, more convenient non-invasive health tests that yield insights into the development of a wide range of diseases.

Prof Owen and his University of London team are looking at how the shape and size of retinal vessels may relate to heart disease and diabetes. Using software that the institute developed, the team is analysing thousands of images from participants in UK Biobank, a research charity that has recruited 500,000 volunteers for a project that aims to improve the prevention, diagnosis and treatment of serious illnesses.

With UK Biobank data, the university is exploring whether changes observed in retinal vessels are occurring before the onset of disease, allowing early detection and chances for prevention. "Those retinal eye vessels are part of the vessels of the body," Prof Owen notes. "If we can look at those directly, it might give us clues as to what's happening to vessels elsewhere in the body — that's why it's considered a potential marker of systemic disease."

> 'A high street optometrist could get an image of your eye sent off for analysis'

Eye scans might be used to detect early stages of Alzheimer's. Researchers at Moorfields Eye Hospital and the UCL Institute of Ophthalmology in London have found a link between thinning of the retinal nerve and poor cognitive ability, a sign of early stages of this form of dementia.

Beyond the retina, other eye abnormalities can indicate the start of life-threatening illness, says Kausik Ray, professor of public health at Imperial College School of Public Health in London. Drooping eyelids could indicate a neuromuscular disorder in someone whose only symptom is fatigue. "It might be a subtle sign, but the only thing you see," he says.

An eyeball turned in slightly towards the nose might, he adds, indicate a brain tumour, which stretches the nerve connecting to it. Double vision possibly indicates a brain tumour, which causes increased intracranial pressure.

Optometrists could play a key role. "You could go to a high street optometrist, get an image of your eye sent off for analysis or preferably analysed there and then," says Prof Owen. In combination with data such as body mass index, blood pressure and age "we could better discern those likely to develop disease."

The barrier to going to an optometrist for broader advice is not cost or absence of technology but lack of knowledge of what is available. "Most people go to these places because their glasses are broken or they're having difficulty seeing," Prof Owen adds. "We need to raise awareness among the general public."

Eye tests as a routine preventive screen might not just save lives, but also huge sums of money for health services by catching diseases before they have progressed. "That's what we should be thinking about," says Prof Ray. "Otherwise it's a missed opportunity."

Market visionaries spot promise in fading powers of sight

Biotech

Attractions grow for early-stage entrepreneurs and venture capital investors, writes *Nuala Moran*

Eyecare is attracting growing interest from early-stage biotech entrepreneurs and venture capital investors. Last month, French biotech specialist Eyevensys closed a $10m first round funding, bringing total venture capital raised by ophthalmology start-ups in the year to date to $143m, notes online news service BioWorld Today.

US funding for ophthalmology companies was $1.9bn in the decade from 2006 to 2015, trade body Biotechnology Innovation Organisation reports. That was 5 per cent of total US venture investment in biotech.

The figures do not paint a full picture, however, because companies developing technologies for a number of disease areas have ophthalmology products in their portfolios. Apellis, a US company specialising in complement inhibition, a form of immunotherapy, raised $47m in February. Among the uses the funds will be put to is developing a treatment for dry age-related macular degeneration, a precursor to wet AMD, a leading cause of vision loss among elderly people.

Venture capital investors cite several attractions of ophthalmology. Not least, eye disease is as much a part of growing old as memory loss and osteoarthritis. Biotech has developed very commercially successful treatments, notably antibody drugs for controlling wet AMD, which have also been approved to treat diabetes-related eye conditions.

"The success with treating wet AMD and diabetes complications underlined the value of the ophthalmology market," says Robert Tansley at Cambridge Innovation Capital, Cambridge university's venture capital fund. "People have made money."

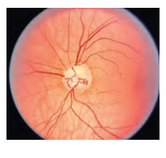
M&A involving eyecare companies has delivered good returns for venture capital backers. Examples include Fovea Pharmaceuticals' $538m sale to Sanofi and ESBATech's acquisition by Alcon for $589m.

Silicon Valley Bank cites eight mergers and acquisitions of ophthalmology start-ups between 2013 and June 2016, while 11 companies completed initial public offerings.

Biotechs with the ambition to do so have a reasonable chance of commercialising their products, argues Omar Amirana, senior vice-president at Allied Minds in Boston, Massachusetts, and chief executive of SciFluor, which is developing a treatment for AMD. "Small companies with good products will get support to get to market," he says.

In gene therapy, companies are working to correct inherited eye disorders by administering a correct copy of a faulty gene, thus promoting the production of a beneficial protein. The cells in the retina are long-lasting and relatively few in number, making the eye a good proving ground for gene therapy.

ViewPoint Therapeutics, headquartered in San Francisco, aims to provide an alternative to surgery for treating cataracts, the leading cause of vision loss and blindness. Cataracts form as crystallins, the main structural proteins in the lens of the eye, become unstable and aggregate, causing the lens to lose its transparency. ViewPoint is developing eye drops that stabilise crystallin, preventing aggregation.



With glaucoma, the aim is to treat the build-up of fluid and pressure in the eye with far simpler procedures

Conversely, in glaucoma the market is shifting from drugs to devices, as eye drops are replaced with surgically implanted micro stents to drain away the fluid that is the root cause of the disease. One of the pioneers is Glaukos in California, whose iStent is designed to be inserted during cataract surgery in glaucoma sufferers.

Glaucoma, the second leading cause of vision impairment, is a progressive condition in which a build-up of fluid increases pressure in the eye, damaging the optic nerve. The intention is that a single procedure could replace decades of daily use of eye drops.

Other companies are developing extended release versions of existing glaucoma drugs. ENV515, produced by North Carolina-based Envisia Therapeutics, is a nanoparticle slow release version of travoprost, the active ingredient in glaucoma eye drops. The aim is to control pressure within the eye for six months at a time with a single injection.

"In other conditions, there is an emerging interplay of therapeutics and devices," says Genghis Lloyd-Harris, partner at London venture capital firm Abingworth. He points to Avedro, based in Waltham, Massachusetts, which has developed a combination treatment for keratoconus, a progressive thinning of the cornea that causes blurred vision.

The treatment involves administering eye drops which, activated by exposing the eye to ultraviolet light, promote cross-linking of collagen molecules.

The process restores the cornea's structural integrity and strength. Avedro's combination of drug and device provides very fine control over collagen cross-linking. It is developing the technique as a non-invasive alternative to laser surgery in treating myopia, or short sightedness.

Pioneering techniques lead drive to prevent blindness

Cell and gene research

Clinical trials of experimental therapies are already under way in patients, writes *Clive Cookson*

The eye is a tempting target for researchers developing innovative stem cell and gene therapies. It is small, easily accessible, biologically well understood and transparent, so the effect of treatment can be evaluated non-invasively.

It is also "immune privileged" to some extent, meaning genetically different cells are less likely to be rejected than in most other tissues. Since we have two eyes, furthermore, the ophthalmologist can carry out a procedure on one while leaving the other untreated as a basis for comparison.

A growing need exists for better treatments. Millions of people worldwide have lost some or all of their sight through diseases ranging from the common age-related macular degeneration (AMD) and diabetic retinopathy to a host of rare genetic conditions.

The Cell and Gene Therapy Catapult, set up by the UK government to promote the technology, says ophthalmology is the most popular field for pre-clinical cell and gene therapy research, accounting for 14 out of 60 UK studies in all areas. These experimental therapies are judged to be three years or less from starting clinical trials in patients.

Six cell and gene therapies for the eye are already in the clinic in the UK out of a total of 57 trials, making ophthalmology the third most popular area for clinical study behind cancer and neurology.

Cell therapy involves the injection of new cells to repopulate a retina depleted by disease. Gene therapy aims to restore the function of existing cells by correcting genetic defects.

No ophthalmic gene or stem cell therapy has yet received full marketing approval anywhere in the world. Most advanced, says a recent review by researchers at the University of Massachusetts, is Spark Therapeutics based in Philadelphia. Spark's lead product treats Leber's congenital amaurosis 2 (LCA2), a form of retinal degeneration caused by a defect in a gene called RPE65. It uses adeno-associated virus (AAV), which infects humans without causing disease, to carry a functioning copy of the RPE65 gene into retinal cells.

If the final phase of clinical trials confirms the improvements shown in earlier patients, the RPE65 product could be approved and launched in 2017. It "is expected to become the first approved gene therapy product [of any sort] in the US, marking a pivotal step for the entire gene therapy field", notes the University of Massachusetts review.

> 'In ophthalmology we need to move on from trying to treat end-stage disease and treat earlier and better'

While Spark is developing gene therapy for the liver and central nervous system as well as the eye, NightstaRx, a UK biotech company spun out of Oxford university in 2014, concentrates on ophthalmology. It, too, uses AAV, the most popular vector for gene therapy, to carry a correct copy of a defective gene into retinal cells.

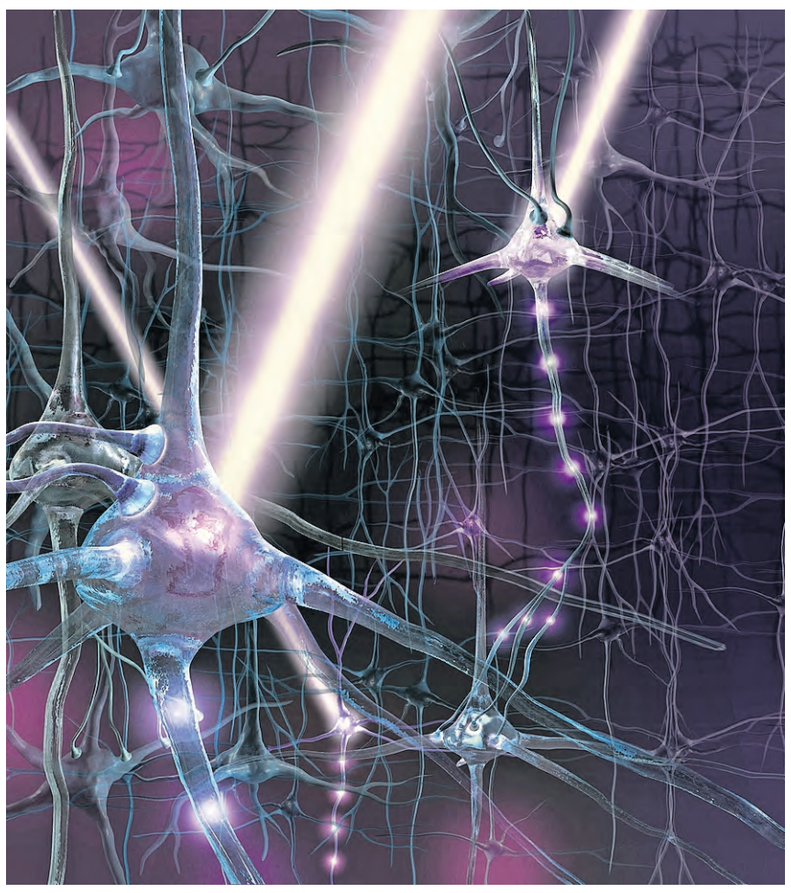
London-based NightstaRx's lead product delivers a type of the REP1 gene to treat choroideremia, an inherited form of progressive blindness. A study of six patients, published this year in the New England Journal of Medicine, found that the therapy maintained or improved vision in the treated eye while the untreated eye continued to deteriorate.

The commercial appeal of ophthalmic gene therapy was shown last month when Allergan, the Dublin-based pharmaceutical group, bought RetroSense Therapeutics, a private Michigan company, for $60m cash and the promise of future milestone payments.

RetroSense is pioneering the clinical application of optogenetics — making cells in the eye sensitive to light. Its RST-001 experimental therapy delivers the ChR2 gene to make retinal ganglion cells respond to light, compensating for the loss of natural photoreceptor cells in degenerative eye disease. The approach is being tested on patients with retinitis pigmentosa, which affects some 100,000 people in the US.

Cell therapy has attracted more public attention than gene therapy for the eye, because stem cells — and embryonic stem cells in particular — are more newsworthy than genetic vectors, even though far fewer patients have received them in clinical trials.

An early stem cell pioneer was Advanced Cell Technology of the US. It changed its name in 2014 to Ocata and was acquired in February 2016 by Astellas, the Japanese pharmaceuticals group, which is continuing its ophthalmic programme on a fairly small scale.



Optogenetics: tests offer hope to thousands of people — Getty Images/Science Photo Library RM

In the UK, the London Project to Cure Blindness launched a clinical trial in September 2015 of a stem cell treatment for wet AMD at Moorfields Hospital in a partnership with the UCL Institute of Ophthalmology and Pfizer, the US drug company. Patches of new retinal pigment epithelial (RPE) cells, derived from embryonic stem cells, have been transplanted into the eyes of two patients to replace those lost in AMD.

Professor Pete Coffey of University College London, co-leader of the project, says clinical results from the first two patients will be published soon and he hopes the trial will be extended to ten people, as originally planned. Pfizer says more cautiously that there are "no current plans to enrol additional patients in this trial".

The next UK clinical trial of ophthalmic cell therapy may come from Professor Alan Stitt at Queen's University Belfast, working with the Cell and Gene Therapy Catapult and Scottish Blood Transfusion Service. His team is generating "endothelial progenitor cells" from umbilical cord blood. These would restore the vasculature (network of blood vessels) within the retina, which goes wrong in ischemic eye disease.

"In ophthalmology we need to move on from trying to treat end-stage disease," says Prof Stitt. "We want to use these new therapies to treat earlier and better, to prevent blindness."

Drugmakers respond to huge need for treatments

Continued from page 1

Large companies are not alone in leading the charge. As with other areas of the industry, it is often smaller biotech groups that are developing the most exciting treatments. Shares in Aerie Pharmaceuticals, which is testing a glaucoma treatment, have jumped by more than 200 per cent in the past six months, after success in clinical trials paved the way for Aerie to seek approval for Roclatan. When added to another drug, Latanoprost, Roclatan reduces the pressure caused by glaucoma, which can lead to blindness if left unchecked.

Perhaps the most exciting area of eyecare is the emerging field of gene therapy, whereby genetic material is inserted directly into a person's cells in order to treat or prevent a disease. The eye is "an almost perfect target for gene therapy", Dr Gilly says. "We are born with a pool of retina cells that are not renewed in our lifetimes. So when you transfer genes into those cells they will probably last for the rest of our lives — and it is quite easy to inject genetic material directly into the eye."

GenSight Biologics has just started a late-stage clinical trial of a drug for Leber's hereditary optic neuropathy, which affects people aged between 15 and 25. It is a brutal, sudden disease causing vision loss in both eyes, with a 98 per cent probability that sufferers will experience complete loss of vision within a year. It affects more than 1,400 people a year in Europe and the US. In a smaller study, GenSight proved the drug could restore vision to the extent that patients were able to read three lines of previously illegible letters on a chart similar to that used by most opticians.

8m
By 2050, number of people in US expected to suffer visual impairment

80m
By 2020, number of people in the world expected to have glaucoma

Such an improvement in letter reading is the gold standard for companies aiming to secure approval for drugs for vision loss but some believe it is not ideal for people with severe forms of blindness. For many of these patients, the ability to make out objects and colours, and to avoid bumping into things, would be a life-altering improvement. The US Food and Drug Administration has therefore recently approved some more creative clinical trial designs.

Spark Therapeutics, a US company developing gene therapies, is testing a treatment for a rare retinal disorder in a late-stage clinical trial. Rather than letters on a chart, it uses a functional vision test where people are asked to make their way around a maze without walking into various objects.

Big questions remain about the long-term success of gene therapies and there are signs that their effectiveness may fade after several months. Yet some large pharma groups appear ready to dip their toes in the water. Allergan recently paid $60m to buy RetroSense, a small gene therapy group that aims to restore light sensitivity to people with the disease retinitis pigmentosa.

Implants point way to living life with your eyes closed

Technology A range of innovations is helping doctors restore vision, reports *Madhumita Murgia*

At 81 years of age, British pensioner Ray Flynn can see with his eyes closed. Last year, the former factory supervisor from Manchester was almost completely blind but this summer he became the first person to receive a bionic eye implant to restore his lost vision — without the need for his own eyes.

Mr Flynn was diagnosed eight years ago with age-related macular degeneration. AMD results in the total loss of central vision and affects half a million people in Britain. He could only see out of the corner of his eyes and was unable to get on with activities like weeding his garden or watching football.

He recently had a £150,000 artificial retina implanted, which receives images from a miniature camera mounted on special glasses. The pictures are transformed into electrical pulses that are sent wirelessly to a chip attached to the back of the retina.

This stimulates his working retinal cells, which send a message to the brain. Because the camera and implant act as his eyes, this means he can see outlines of images even with his own eyes closed. With time, he can train his brain to interpret the images more clearly.

The implant, known as Argus II and manufactured by US company Second Sight, is one of a range of innovations that are helping doctors restore vision. Argus II has been implanted in more than 150 patients across the US and Europe who have the rare inherited condition of retinitis pigmentosa.

A system developed by Monash University scientists in Australia can bypass the eye completely. An external camera feeds image information directly to the brain via a neural chip, using a technology potentially able to help more than 80 per cent of clinically blind people to see visual outlines or patterns. A first human implant is expected this year.

Digital developments to treat blindness are not just happening in well-funded laboratories in wealthier regions of the world. Hubs of innovation exist in developing countries such as India.

At the LV Prasad Eye Institute in Hyderabad nearly 15m people have been treated for serious eye conditions, half of them free of charge. It is responsible for research on pioneering ways to improve vision, including 3D printed eyes, grow-your-own cornea techniques and bionic implants. The institute runs the largest eye bank in Asia, implanting more than 40,000 corneas a year from organ donors.

"What is unique about our network of hospitals is we try to treat all patients that need us, irrespective of whether they can pay or not," says Virender Sangwan, director of LV Prasad's stem cell centre and innovation labs. "We develop technologies so our treatments can be scaled up to provide access in rural parts of India."

Dr Sangwan's team focuses on corneal blindness, a cluster of conditions that affect about 12m people globally, a quarter of them in India. Although transplanting donor corneas is the most straightforward method, it is dependent on having a steady supply of healthy human corneas, donated by people who have recently died.

"Bio-synthetic cornea will eliminate the supply-side problem," Dr Sangwan adds. "If we can create artificial corneas, that will significantly improve the lives of millions." He is collaborating with researchers at Sweden's Linköping university to design a new material, similar to human collagen, that is cheap and easy to synthesise in a lab. The material will be used to create artificial corneas and has been tested in animals. It starts human trials in early 2017.

The corneas could ultimately be assembled by 3D printers. Dr Sangwan says his institute is in talks with printing pioneers such as Pandorum, a Bangalore-based start-up specialising in 3D printing of human tissues such as livers.

Beyond implants, companies such as Google, Samsung and Intel are working on designs for smart, connected contact lenses. Google's life sciences arm Verily, in partnership with Swiss multinational Novartis, plans to test a prototype on humans this year. This lens is supposed to correct vision in people with presbyopia, or age-related farsightedness, helping them focus between long- and short-range vision.

This year, Columbia University scientists found that smart contact lenses, from Swiss company Sensimed, were the best clinical tool to measure progression of glaucoma. Sensors in the lenses can detect changes in the eye's internal pressure over an extended time, rather than just by way of a snapshot measurement when a patient comes in for a visit, as users wear them continuously. This gives clinicians clues as to how fast the glaucoma is developing. "With this device we can see the changes that occur over 24 hours, which is the best clinical predictor of progression," says Gustavo De Moraes, associate ophthalmology professor at Columbia.

> 'If we can create artificial corneas, it will improve the lives of millions'

Eventually we may even be able to exploit digital implants in eyes that never tire and connect to smartphones. Google filed a patent this year for an injectable artificial lens with sensors that enhance sight and stream data. Conceivably, it would enable us to read electronic bar codes and sense irritating allergens, allowing timely treatment.

Bionic man: Ray Flynn of Manchester was the first person to undergo this type of surgery — Peter Byrne/PA Images

Surgical equipment Lasers are with us, robots on their way

The surgery is fiddly. Making tiny, precise incisions in the inside of the eye requires extreme skill. Surgeons need to slow down their pulse and time movements between heart beats to avoid the smallest of hand tremors. Today, lasers are the most frequently used technology in surgeries ranging from cataract operations to corrective vision procedures.

Among the most sophisticated is the ultrafast femtosecond laser. It is used as an alternative to other manual techniques in the tearing of the eye's lens capsule in cataract surgery, or cutting a corneal flap during so-called Lasik eye surgery. Surgical methods that involve lasers are also being improved to provide better control. A 3D visualisation system, designed by Novartis subsidiary Alcon, helps guide surgeons through the procedures of retinal operations.

Florida-based Lensar's laser is used for corneal incisions and cataract operations. Lensar says it uses augmented reality, similar to the Pokémon Go game that overlays characters on to the real world, to reconstruct a detailed 3D model of the anatomy of each patient's eye to help in preparation for operations.

The first robotic operation inside the eye took place recently at the University of Oxford's John Radcliffe Hospital. Once robotic surgery was not feasible at the microscopic level required but, in September, Oxford surgeons used a remotely controlled robot to lift a membrane 100th of a millimetre thick from the retina at the back of a patient's right eye.

To counter the surgeon's tremors, the operation took place through a hole less than 1mm in diameter. Dutch company Preceyes built the robot, the like of which may in the future help speed up cataract surgery and perform tasks that human hands cannot do, such as injecting drugs or stem cells into retinal veins, which are thinner than human hair. **MM**

Contributors

David Crow
FT senior US business correspondent

Denis Schluppeck
University of Nottingham associate professor (neuroscience and vision)

Sarah Murray
Freelance journalist

Nuala Moran
Freelance science journalist

Madhumita Murgia
FT European technology correspondent

Clive Cookson
FT science editor

Andrew Jack
FT head of curated content

Brian Groom
Freelance journalist and former FT UK business and employment editor

Steven Bird
Designer

Alan Knox
Picture editor

Peter Chapman
Commissioning editor

River blindness parasites 'play long game'

Aid A campaign to eliminate the disease has scored significant success in Latin America, while Africa continues to carry a heavy burden, reports *Andrew Jack*

Treatment: organisers look to conquer river blindness in Africa and Latin America over the next decade — Kay Hinton/Tom Saater/Peter DiCampo

Roy Vagelos remembers the thrill in the 1980s when he saw test results of his company's prototype drug against river blindness and the parasitic worm, Onchocerca volvulus, that causes pain, scarring and blindness in hundreds of thousands of people across Africa and Central and South America.

Scientists at Merck led by William Campbell — who last year shared the Nobel Prize for medicine for the work — showed that a variant of avermectin, a drug originally developed to combat parasites in dogs, could prove effective in tackling onchocerciasis in humans. Under Mr Vagelos, who from the position of head of research had been appointed Merck's chief executive, the company would launch a programme to donate as much of the drug as was required for as long as necessary.

"It was one of the most exciting results we had ever seen," Mr Vagelos recalls, looking back on his time at Merck. "I was a physician who switched to basic research, then drug discovery, as a way to close the loop to get important new drugs to treat people beyond the normal small groups a doctor can help."

Yet more than three decades after Merck began its programme, the burden of the disease remains heavy, raising questions about whether international goals for its elimination by 2025 are realistic.

Little doubt exists about the continued need for the drug, called ivermectin or Mectizan, or some improved version of it. Onchocerciasis affects an estimated 37m people, nearly all in Africa.

It occurs close to fast-flowing rivers, breeding grounds for blackflies whose bites transmit the worms. These grow into adults (macrofilariae) in humans and cluster in nodules, where they produce large quantities of young worms (microfilariae) some of which are transmitted back into flies.

The microfilariae cause inflammation leading to severe itching, loss of vision and sometimes epilepsy and premature death. The stigma of the disease forces infected people to emigrate from fertile land and cuts productivity.

Large-scale programmes to spray insecticides to kill the flies in the 1970s had some success but lost momentum. In the absence of government funding, Merck has donated treatments since 1987 — 176m last year — and has provided an average additional $5m annually to help with delivery.

In South and Central America, efforts to eliminate the disease have proved successful everywhere except a stretch of the Amazon between Brazil and Venezuela. In Africa, progress has been far slower and concentrated instead on control of the disease. Sharp reductions in the disease's burden have been recorded in Niger and Malawi.

'Mectizan has been phenomenally successful, saving the sight of millions'

One measure required is to raise the frequency of Mectizan use across Africa from once to twice or even four times a year. "The time is now," says Frank Richards of the Carter Centre — the non-profit founded by former US President Jimmy Carter and his wife Rosalynn — and a veteran of the treatment programmes.

Although Mectizan is generally safe, it is dangerous to patients in some parts of Africa who are infected with the disease loa loa, commonly known as "eye worm". Given that some evidence exists of emerging resistance to the treatment, scientists are seeking new drugs.

"Mectizan has been phenomenally successful, hugely reducing the burden and saving the sight of millions," says Robert Don from the Drugs for Neglected Diseases Initiative, a charity involved in several research programmes. But, he adds, "we need a toolbox of improved drugs, diagnostics, sanitation and vector control."

Supplies of Mectizan are vulnerable to such as "distributor fatigue" among the largely unpaid community volunteers who administer drugs to local people. Capacity and expertise to kill the insects is limited. Civil wars and other political unrest reduce opportunities to fight the disease in several countries.

The extent of the World Health Organisation's support prompts some scepticism. Last year, its programme for onchocerciasis control was abolished. The Expanded Special Project for Elimination of Neglected Tropical Diseases that replaced it has a remit far beyond river blindness and less funding.

"When demand is there, supply has always been, too," says Ken Gustavsen, who runs Merck's Mectizan donation programme for both onchocerciasis and lymphatic filariasis, which also uses the drug in combination with others. "We're still aiming for onchocerciasis elimination by about 2025."

"We need more flexible approaches," Mr Richards cautions. "These parasites want to play the long game. They wait for us to tire."

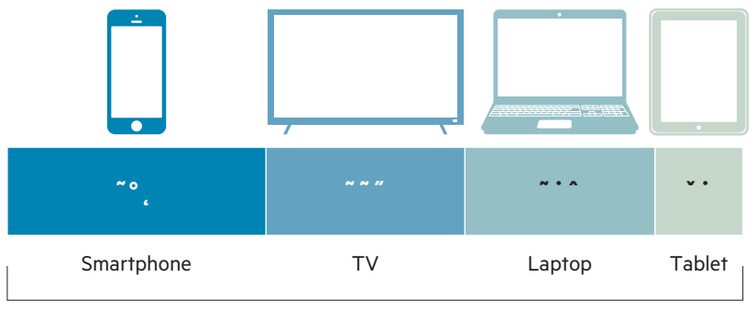
Think how you blink and other tips for the digital age

Vision syndrome

Many people spend more time staring at devices such as smartphones, laptops and tablets than they do sleeping, writes *Brian Groom*

Daily screen use

In minutes



Total: °˜ ^
(two minutes short of seven hours)

Source: MillwardBrown

The amount of time people spend looking at screens has grown dramatically, from using computers at work to watching television at home and being glued to a smartphone or tablet most of the day. It is a wonder how little trouble this appears to be causing our eyes.

The number of people complaining of tired, dry or sore eyes — some optometrists call this "digital eye strain" or "computer vision syndrome" — has risen but experts note that little reliable evidence exists of longer-term damage.

While smartphone and tablet use has greatly increased the average person's exposure, says Chris Hammond, ophthalmology professor at King's College London, "we are not seeing any epidemics of eye problems related to that".

He does, though, recommend limiting children's screen use because the phenomenon of pre-school children spending hours on phones and tablets is recent and effects are unknown.

Globally, a 16-45-year old typically spends 418 minutes — two minutes short of seven hours — a day looking at screens, say researchers Millward Brown (*see graphic*). This comprises watching television, using the internet on a laptop or personal computer and viewing smartphones and tablets.

Smartphones have become the world's largest screen medium. Combining smartphone minutes with tablet use, mobile devices account for nearly half of all screen time.

In many cases, people may spend longer on screens than they do sleeping. Figures range from 317 minutes in Italy to 540 in Indonesia. The average US user clocks up 444 minutes (480 in China, 411 in the UK).

One concern has been the effect of high-energy visible light — "blue light" — emitted by devices. Laboratory studies suggest that high levels of exposure can damage retina tissue. But Prof Hammond, who sits on the scientific committee of the Royal College of Ophthalmologists, says there is no evidence that low levels of blue light are harmful: "The energy level emitted by phones and iPads is extremely small. Even on a grey day outside, your blue light exposure is something like 30-fold more than looking at a tablet or a screen."

Some evidence does show that using screens before going to bed disrupts the circadian cycle, or sleep-wake cycle, since blue light inhibits release of melatonin, the hormone that makes us sleep. Daniel Hardiman-McCartney, clinical adviser at the UK's College of Optometrists, advises people not to use devices for an hour before they go to bed.

Another concern is myopia among children. A big increase in short-sightedness has emerged particularly in urban east Asia where children spend a lot of time reading and little time outdoors. Research results this year from the UK College of Optometrists and University of Ulster say 16.4 per cent of UK children are myopic, compared with 7.2 per cent in the 1960s.

Studies in Australia and the US indicate that spending time outdoors protects children against myopia. Some people suggest there may be a link between the condition and close-up work, though that could apply to books as well as screens. Prof Hammond says close-up work seems not to be the problem because indoor activity in sports halls does not protect children either, whereas outdoor activity does.

'We now spend the vast majority of our day looking at things less than one metre away'

That leaves eye strain as the most common problem. Some 50-90 per cent of people who work at computer screens have symptoms of "digital eye strain", say studies. This can include dry, sore eyes, headaches or blurred vision.

"We are now spending the vast majority of our day looking at things less than a metre away," says Mr Hardiman-McCartney. "Our eyes are not designed to focus that close."

Even a small defect in vision can lead to strain as the eyes seek to compensate. If your eyes do not work well together, looking at a screen all day can cause headaches. People also tend to blink incompletely when they stare at a screen, which can lead to dryness.

Productivity may be affected if eye strain causes workers to read more slowly or make errors. Research by the University of Alabama at Birmingham's School of Optometry has suggested that uncorrected vision problems could reduce work rate by up to 29 per cent.

Optometrists recommend frequent breaks or the 20-20-20 rule: every 20 minutes, look 20ft away (6m) for 20 seconds to give your eye muscles a break. Also, they say, make sure to take full blinks.

Mr Hardiman-McCartney says people need to sit upright at screens with eyes looking down at about 45 degrees, adjust brightness to the lowest level at which they can see a screen clearly and use a text size large enough to read. They should also have regular eye tests.