outline

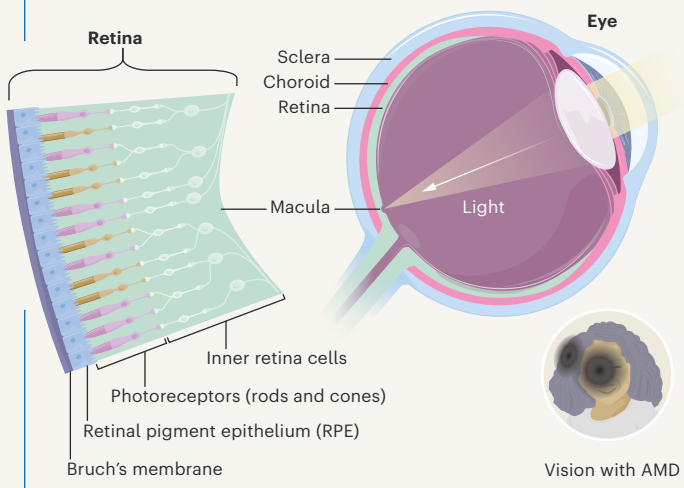
ROUTES TO RETINAL REPAIR

People who develop the dry form of age-related macular degeneration (AMD) currently have no effective options for preserving their vision. But several promising therapeutic avenues are being explored that might just change that.

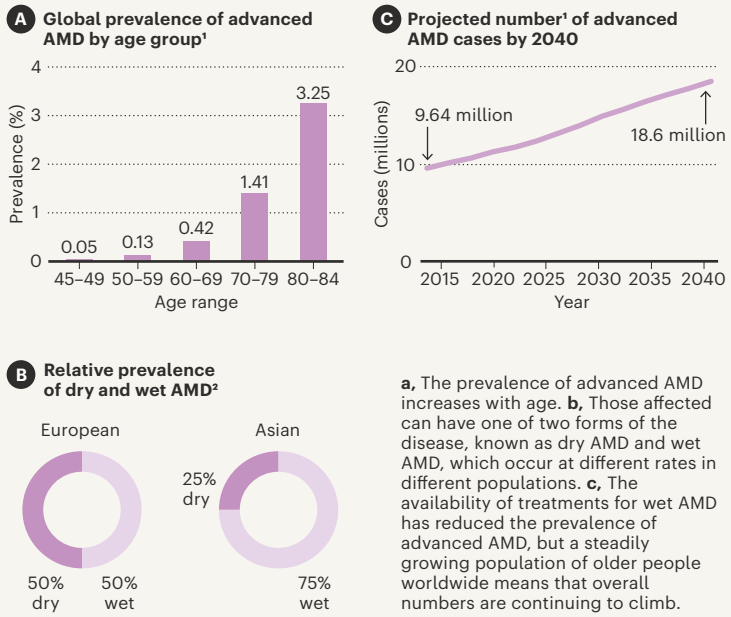
By **Michael Eisenstein**; *infographic by* **Lucy Reading-Ikkanda**

THE FOCAL POINT

The highest density of light-detecting photoreceptors can be found in a 5-millimetre patch of the retina called the macula. This ultra-sensitive cluster of rods and cones captures the central part of our visual field, and is responsible for filling in the fine details of the objects we see. The progressive loss of cells in the macula in AMD causes vision to become gradually impaired, leading to blindness.



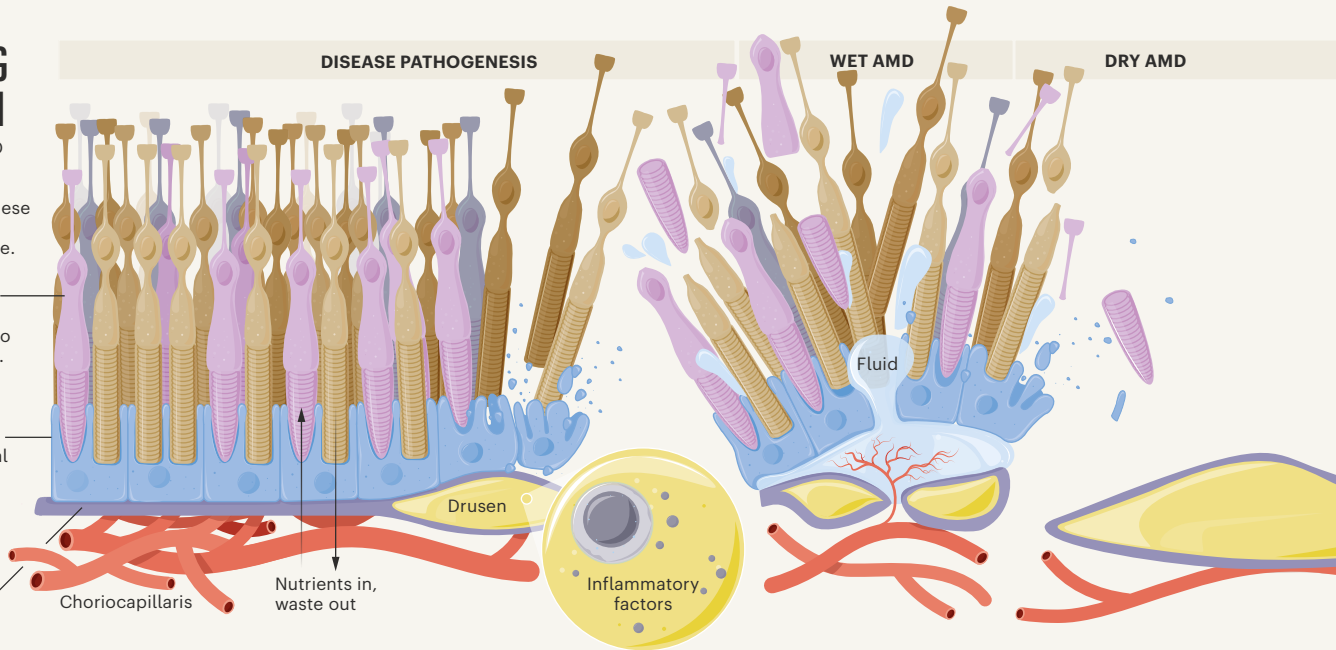
AN EVER-GROWING PROBLEM



a, The prevalence of advanced AMD increases with age. **b,** Those affected can have one of two forms of the disease, known as dry AMD and wet AMD, which occur at different rates in different populations. **c,** The availability of treatments for wet AMD has reduced the prevalence of advanced AMD, but a steadily growing population of older people worldwide means that overall numbers are continuing to climb.

AN ERODING ECOSYSTEM

Wet and dry AMD begin in similar ways, but the pathologies of these two conditions ultimately diverge.



As we age, blood vessels in the **choriocapillaris** become more sparse. This is thought to be an important starting point for AMD.

Deposits of lipids, proteins and cellular waste, known collectively as **drusen**, form in Bruch's membrane, blocking transit between the RPE and the vasculature.

An inflammatory response is activated. Genetic factors and smoking can exacerbate this process.

In people with **wet AMD**, blood vessels form around the drusen and leak fluid into the eye. Several treatments exist for wet AMD.

In **dry AMD**, extensive loss of the choriocapillaris, RPE and photoreceptors — a state known as geographic atrophy — results in the onset of blindness.

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HOW TO RESTORE A RAVAGED RETINA

People with dry AMD currently have no effective treatment options to restore lost vision or prevent its decline. But insights into the molecular and cellular pathology of this condition have guided the development of several promising avenues for intervention. These treatments are all still undergoing testing in clinical trials, but have shown some potential to slow or halt dry-AMD progression.

ENDING IMMUNE ATTACK

The complement system is a complex signalling cascade that ramps up the immune response to infection or injury. Mounting evidence[3] links one arm of this system — the 'alternative pathway' — to AMD. Some treatments[4] target the hub of the complement system, the C3 protein, whereas others aim at less-pivotal factors that could achieve more specific effects.

Pegcetacoplan is a C3 inhibitor that has slowed dry AMD progression in some clinical trials. Two recent phase III studies yielded mixed results[5], but the company behind the drug intends to file for regulatory approval.

GT005 is a gene therapy that delivers a gene encoding a C3 inhibitor to the RPE.

Avacincaptad pegol blocks the function of C5, which is downstream of C3. It reduced dry AMD progression by around 28% in a phase II trial[6], although participants exhibited an increased risk of wet AMD. The drug is now in a pivotal phase III trial.

REBUILDING A COMMUNITY

By coaxing embryonic stem cells (ESCs) to develop into healthy RPE cells, researchers can potentially bolster the health of retinal tissue that would otherwise succumb to geographic atrophy.

Injection of ESC-derived RPE cells into the eye stabilized or improved vision for nine people who received treatment in a phase II trial for at least six months after transplant[7].

Another approach is to seed ESC-derived RPE cells onto a synthetic surface resembling Bruch's membrane and transplant them as a pre-organized sheet.

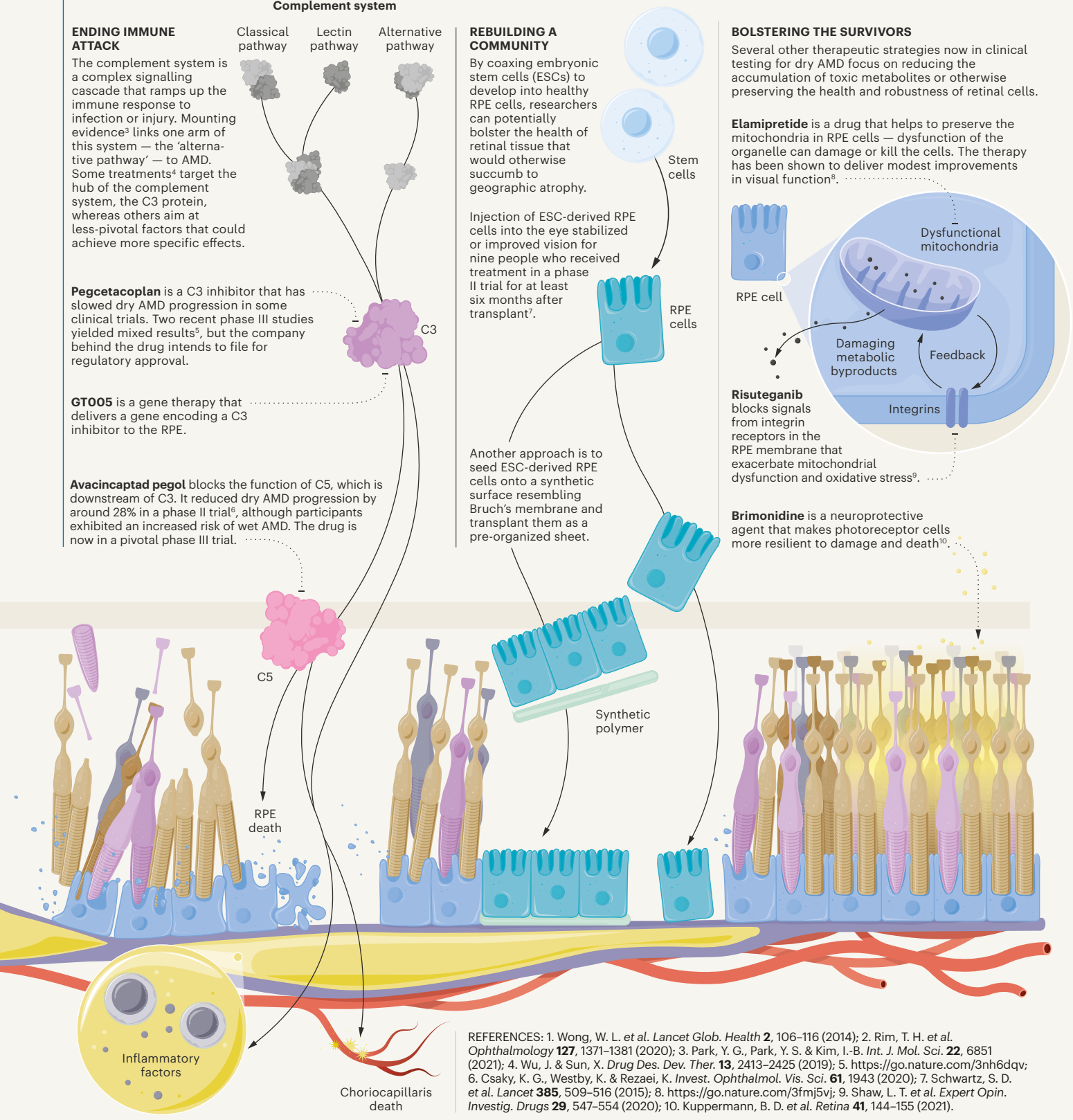
BOLSTERING THE SURVIVORS

Several other therapeutic strategies now in clinical testing for dry AMD focus on reducing the accumulation of toxic metabolites or otherwise preserving the health and robustness of retinal cells.

Elamipretide is a drug that helps to preserve the mitochondria in RPE cells — dysfunction of the organelle can damage or kill the cells. The therapy has been shown to deliver modest improvements in visual function[8].

Risuteganib blocks signals from integrin receptors in the RPE membrane that exacerbate mitochondrial dysfunction and oxidative stress[9].

Brimonidine is a neuroprotective agent that makes photoreceptor cells more resilient to damage and death[10].



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