IMPLANTED BIOMATERIALS

A gelling vitreous replacement

A rapidly gelling, biocompatible co-polymer, tested in rabbit and non-human-primate models of retinal detachment, makes for an effective replacement of the damaged vitreous.

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The risk factors of retinal detachment (RD) — which has an overall incidence of 1 to 5 cases per ten thousand people, although in some patient groups it can be as high as 0.5% (one case per 200 patients) — include myopia, previous cataract surgery and severe eye injury. The impact of this condition on quality of life is serious, with only 40–50% of eyes regaining central vision (also called reading vision) following successful surgical repair of a detached retina that involves the macula. Air, expanding gases[1] or silicone oil[2] have been used for the treatment of RD for over five decades, with over 90% of eyes gaining retinal reattachment. However, these vitreous replacements have limitations. On the one hand, patients who have undergone vitrectomy (the surgical removal of the vitreous from the eyeball) with the use of gases have limited vision while the gas is still present, and are not allowed to fly or travel to high altitudes because of the possible expansion of gas and, therefore, the elevation of eye pressure. On the other hand, eyes receiving silicone oil need to undergo another operation after 3 to 12 months, to remove the oil. Also, silicone oil may emulsify and result in glaucoma, which often persists after oil removal. These patients typically find that the most difficult aspect of their recovery is the required constant prone positioning of the body. Hence, these patients commonly suffer from spinal discomfort, and occasionally develop elbow and ulnar nerve symptoms from the compression of the ulnar nerve during prolonged prone positioning when their arms are folded to support their head on a pillow.

Attempts to develop natural vitreous replacements, such as collagen or hyaluronans, have not been successful. Recently, there have been attempts to use hydrogels because their properties can be similar to the human vitreous and because they can be easily crosslinked to form a matrix capable of mechanically supporting the retina[3]. Reporting in *Nature Biomedical Engineering*, Xinyi Su, Xian Jun Loh and Gopal Lingam now show, in rabbit and non-human primate models of RD, that a biocompatible thermogelling hydrogel serves as an effective tamponade during vitrectomy, and that it promotes the formation of a vitreous-like body[4].

Su and co-authors used a biodegradable co-polymer derived from combining poly(ethylene glycol) — a hydrophilic polymer — with a thermosensitive polymer (poly(propylene glycol)) and a hydrophobic polymer (poly(ε-caprolactone)). Following crosslinking of the polymer via urethane bonds, it rapidly forms a hydrogel that can be injected through small-gauge instruments. The authors show that the hydrogel has an index of refraction similar to the human vitreous, and that after vitrectomy in rabbit eyes, a hydrogel concentration 7% in weight was biocompatible, according to analyses using optical coherence tomography, electrophysiology and histology. A hydrogel concentration of 3% in weight was found to be toxic, whereas the swelling potential of a hydrogel concentration of 12% in weight may have caused rises in intraocular pressure. Two non-human primates tolerated the hydrogel concentration of 7% in weight for over 12 months. After 3 months, a proteomic analysis of the vitreous indicated that most of the hydrogel volume had been replaced by native vitreous.

Although RD may occur at any time, it usually develops with age. At birth, the central clear cavity of the eye (the vitreous) is a clear gel consisting of hyaluronans suspended in a collagenous matrix. By the second decade of life, the process of syneresis (or liquefaction) begins, where collagen in the central vitreous starts to coalesce into strands, which are perceived by the patient as 'vitreous floaters' (which appear more conspicuous when seen against a blue sky, white surface or wall, often moving in and out of the visual axis as the eye moves). More serious floaters can develop when the thin layer of the vitreous matrix that is attached to the surface of the retina separates and migrates into the central zone of the vitreous. When this event, called posterior vitreous separation or detachment,

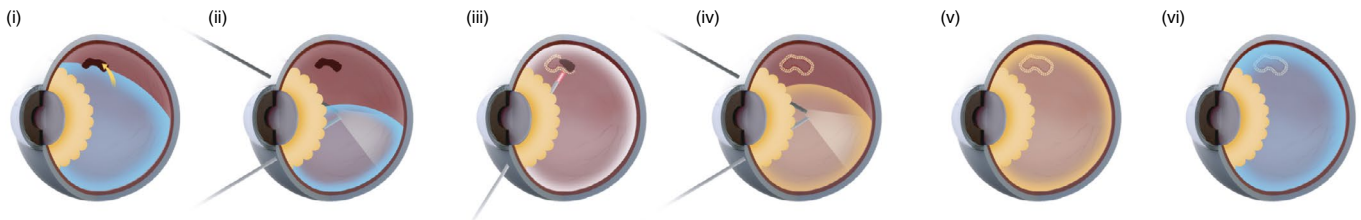

Fig. 1 | Repair surgery in retinal detachment. (i) In retinal detachment with a retinal tear (black), the native vitreous (blue) causes damaging traction forces. (ii) Removal of the vitreous via a vitrectomy probe (bottom probe in the schematic) and with internal fibre-optic illumination (provided by the top probe in the schematic) for visualization. An infusion cannula (not drawn) is also typically used. (iii) Application of laser light around the retinal tear after the exchange of fluid and its replacement with air (white). (iv) Injection of the thermogelling hydrogel (yellow), which acts as a tamponade agent. (v) The thermogel, which supports the retina, allows for adhesion to occur at the site treated with the laser. (vi) As the thermogel degrades, it is replaced by a vitreous-like-body (blue). Figure reproduced from ref. [4], Springer Nature Ltd.

occurs, a retinal tear may develop in roughly 10–12% of eyes. The patient may experience a veil or film over the vision, sometimes accompanied by small dots, arising from bleeding retinal blood vessels that have been torn, or by the perception of lightning flashes (photopsia). Occasionally, significant bleeding can obscure much of the vision. Prompt examination of the patient is important, because retinal tears can lead to RD. Yet, if identified and treated (usually with laser photocoagulation), RD can be avoided.

The repair of retinal detachment usually requires surgery. The traditional approach, still used in select cases, involves the placement of a silicone rubber element under the retinal breaks, which is then sutured to the wall of the eye (scleral buckle). Tears are then treated using a cryoprobe to freeze the retina, and the subretinal fluid is drained by using a fine needle to penetrate the eye wall (sclera). The retinal tears settle back onto the eye wall, and the irritation caused by the freezing treatment stimulates the formation of adhesion around the tear so that vitreous fluid can no longer pass into the subretinal space. Recently, however, retinal detachments are increasingly treated via vitrectomy. In this procedure (Fig. 1), three microinstruments (typically 0.5 mm in diameter) are inserted into the vitreous space: a vitreous cutter, a fibre-optic illuminator and an infusion cannula. The surgeon views the instruments inside the eye through the pupil and lens by using a microscope fitted with custom optics. The vitreous is removed, which relieves traction to retinal breaks. The retinal detachment is flattened by aspirating subretinal fluid through an existing retinal tear, using a liquid with a high specific gravity (typically, perfluorocarbon) or by making a small retinal break to allow the drainage of subretinal fluid (drainage retinotomy). Air is then infused into the eye to fill the vitreous. Under air the tears are surrounded by using a laser probe that emits green light (532 nm in wavelength) or infrared light (810 nm in wavelength). At the completion of the procedure, the air is replaced by a gas–air mixture that will persist in the eye for longer periods than air alone (approximately 5 days). Typically, the gases used are sulfur hexafluoride (SF_6), which lasts approximately 12–14 days, or perfluoropropane (C_3F_8), which lasts between 4–6 weeks. Alternatively, the surgeon may choose to use silicone oil (polydimethylsiloxane). Both gases and silicone are hydrophobic materials that rely on surface tension and buoyancy to act as an effective tamponade. Their high surface tension prevents their passage through retinal breaks while their specific gravity, lower than that of water, exerts a buoyant force against the retina. The buoyant force exerts pressure against retinal tears until the adhesion resulting from the laser treatment is secure. The patient is thus often instructed to maintain their head in a prone position post-operatively for 1–2 weeks. Since both gas and silicone oil rise to the top of the eye when the patient's head is erect, recurrences of RD are more commonly seen in the inferior retina. Prone positioning also keeps the gas bubble or silicone oil away from the lens to prevent the cataractous opacities that develop from prolonged contact. During the post-operative recovery period, visual acuity is also reduced because of the difference in the index of refraction induced by a gas bubble or by silicone oil. Visual acuity is better when silicone oil is present, although patients often describe the appearance as 'seeing through water'. Su and colleagues' hydrogel might replace the final steps of filling the vitreous cavity, where the co-polymer would substitute the gas or silicone oil and its rigidity would keep the retina attached. Also, because the co-polymer hydrogel reabsorbs over three months, with the reformation of a vitreous-like body akin to the native vitreous, it is a promising outcome for the potential use of the hydrogel in the treatment of RD, as it would eliminate the need for head positioning, restore vision immediately, and lead to faster rehabilitation. If so, this would be a disruptive advance in RD surgery. Still, the hydrogel-degradation pathways, the safety of the degradation products, and their interaction with blood, fibrin and other proteins in the eye, should be carefully studied before human clinical trials are started. ❐

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