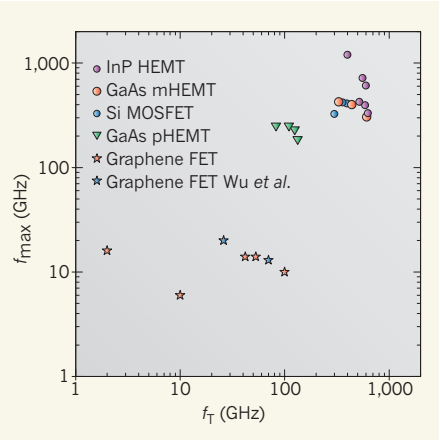

Figure 1 | Frequency performance of graphene transistors. Maximum frequency of oscillation, f_{max}, versus cut-off frequency, f_T, for graphene field-effect transistors (FETs) and competing radiofrequency FETs: indium phosphide high electron mobility transistor (InP HEMT), gallium arsenide metamorphic HEMT (GaAs mHEMT), silicon metal-oxide-semiconductor FET (Si MOSFET), and GaAs pseudomorphic HEMT (GaAs pHEMT). The red stars designate FETs made from 'epitaxial' graphene, whereas blue stars denote Wu and colleagues'[1] FETs, which were made from graphene grown by chemical vapour deposition.

conventional RF FETs, f_{max} commonly improves with shorter gate lengths, but the opposite is the case for Wu and colleagues' graphene FETs.

The main reason for the disappointing f_{max} is the unsatisfying, weak saturation of the device's drain current. Experience with conventional RF FETs clearly shows that, to exploit their full frequency potential, FETs need to be operated in a regime of strong current saturation. One explanation for the weak saturation in graphene FETs is the high electrical resistance between the device's electrodes (source and drain) and its graphene channel[12]. Unfortunately, a reliable way of significantly reducing such contact resistance in graphene devices is still lacking. Another issue that affects current saturation is the fact that graphene lacks a bandgap (an energy range where no electron states can exist). The huge gap between the f_{max} performance of graphene FETs and that of competing silicon and III-V FETs indicates that achieving strong current saturation and low contact resistance is crucial to making graphene RF FETs more competitive, and to open the door to their application in electronic circuitry. Although closing the gap seems hardly possible at the moment, we should remain optimistic and keep in mind the short history of graphene RF transistors and the huge progress made in the field since 2008. ■

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REGENERATIVE MEDICINE

DIY eye

Generation of complex organs *in vitro* is a major challenge in regenerative medicine. But it is not an impossible one: an entire synthetic retina has now been generated from embryonic stem cells. SEE ARTICLE P.51

ROBIN R. ALI & JANE C. SOWDEN

In this issue, Eiraku *et al.*[1] provide a series of extraordinary videos recording the formation of an embryonic mouse eye: for the first time, we see unfolding in real time the beautiful events that shape the early stages of mammalian eye development. But even more remarkable is that these are not recordings from live animals, but of self-organizing three-dimensional (3D) cultures of embryonic stem cells.

By the sixth week of human development, the rudiments of the mature eye are visible: bilayered optic cups, partially encapsulating the lens vesicles, have formed from the eye-field region of the anterior neural plate and the overlying surface ectoderm (Fig. 1). From the inner layer of the cup, the complex laminar structure of the neural retina will develop, with light-sensing photoreceptor cells connecting through interneurons to the retinal ganglion cells whose axonal processes project to the higher visual centres in the brain.

Elucidation of the mechanisms underlying embryonic eye development began more than a century ago. In one of his most significant experiments, Hans Spemann, a founder of developmental biology, showed that if the optic vesicle (the structure that eventually evolves into the optic cup) is destroyed, the lens fails to form. The interaction of the surface ectoderm (from which the lens derives) with the underlying optic vesicle has been considered a classical example of embryonic induction — the process by which one cell group signals to a neighbouring group and influences their future development. An array of genes has now been identified, many of which encode transcription factors or growth factors that are essential for the formation of the optic cup.

The likelihood of growing a complex organ such as an eye in a dish, however, has seemed remote and futuristic, although this distant frontier of regenerative medicine constantly moves closer. In the past decade, inspiring work[2] has shown that expression of eye-field transcription factors can lead to eye formation in unusual locations along the body of *Xenopus* frogs. Moreover, following the generation of human embryonic stem (ES) cells, it has proved possible[3,4] to direct their differentiation towards the retinal lineage and generate both retinal pigmented epithelium (RPE) and retinal neurons (Fig. 1). Cell-culture approaches have mainly sought to maximize the development of specific cell types with the potential aim of transplanting such cells for therapeutic purposes.

In vitro, RPE cells derived from ES cells self-organize into a characteristic simple monolayer. By contrast, reproducing the more complex and precise laminar organization of the neural retina presents a difficult tissue-engineering challenge. But reports describing lens-like structures[5] and retinal progenitor rosettes in ES-cell cultures[6] hinted at some potential for organization of eye tissue *in vitro*.

Now, Eiraku *et al.*[1] (page 51) reveal with startling beauty and remarkable clarity that the complex process of evagination of the optic vesicle, and then its invagination to form the bilayered cup, can occur spontaneously in culture, starting with a population of homogeneous pluripotent cells — cells that can differentiate into any cell type (see Fig. 1 of the paper[1] and the supplementary videos).

The key to this advance was that Eiraku and colleagues did not just simplify their previous[7] differentiation protocol for ES cultures, but also added Matrigel, which includes extracellular-matrix components. Under these conditions, and using a green fluorescent protein (GFP) reporter gene expressed in the eye field and the neural retina, they found that a neuro-epithelium-like layer of GFP-positive cells evaginated from the sides of hollow balls of ES cells, in a process reminiscent of optic-vesicle formation. Over time, the optic vesicles spontaneously underwent dynamic morphogenesis and formed bilayered cups. The cups

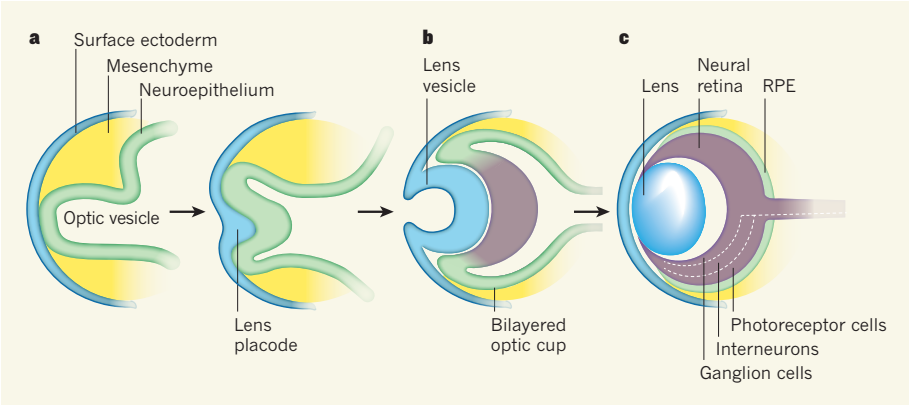

Figure 1 | Eye development. **a**, At early stages of eye development, the surface ectoderm thickens and invaginates together with the underlying neuroepithelium of the optic vesicle. **b**, The inner layer of the bilayered optic cup gives rise to neural retina and the outer layer gives rise to the retinal pigmented epithelium (RPE) (**c**). The mature neural retina (**c**) comprises three cellular layers: photoreceptors, interneurons (horizontal, amacrine and bipolar cells), and retinal ganglion cells. Eiraku *et al.*[1] generated optical cups *in vitro* from embryonic stem cells.

appropriately expressed the distinctive molecular markers of both the neural retina and the RPE, confirming their identity; another indicator was visible as RPE pigmentation.

An even more striking proof that these are genuine retinas is that, in culture, the synthetic optic cups undergo cell differentiation. Indeed, retinal progenitor cells — the multipotential cells of the neural retina — divided and differentiated into all the main retinal neuronal cell types, including photoreceptors. These events seem to follow the normal temporal sequence of retinal tissue formation, and the resulting cells were correctly organized in the appropriate cellular layer.

But even though optic cups can now be grown in culture from ES cells, we still don't fully understand the principles underlying their development. For instance, it is surprising that optic cups can form independently of any interaction of the neuroepithelial cells with surface ectoderm or mesenchymal tissue that would normally surround them in a developing embryo (Fig. 1). Eiraku *et al.*[1] propose that the ES-cell-derived retinal cells have a latent intrinsic order, and that collections of cells can self-pattern and undergo dynamic morphogenesis by obeying a sequential combination of local rules and internal forces within the epithelium.

However, Eiraku and colleagues' powerful *in vitro* system has great potential as it can be manipulated to define the molecular interactions that are essential for eye development. Moreover, if functional outer rod segments — where the protein complexes responsible for phototransduction are located — can be produced in longer-term cultures, this 3D system will be invaluable for functional studies examining the response of the retina to light.

What's more, development of an equivalent human 3D system could offer the prospect of disease modelling and drug testing using induced pluripotent stem cells generated from patients' tissues. Most forms of untreatable blindness result from the loss of photoreceptor cells, leaving other retinal neurons intact. In mice, transplantation of photoreceptor precursor cells isolated from the developing mouse retina can repair adult retinas[8]. A major challenge is to obtain sufficient numbers of photoreceptor precursors at the appropriate stage of development from a renewable cell source. This 3D system for culturing ES cells[1] may solve that problem by providing synthetic retinas at defined stages of development from which precursors can be isolated more readily for use in transplantation. ■

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OCEANOGRAPHY

When glacial giants roll over

The energy released by capsizing icebergs can be equal to that of small earthquakes — enough to create ocean waves of considerable magnitude. Should such 'glacial tsunamis' be added to the list of future global-warming hazards?

ANDERS LEVERMANN

About half of Greenland's annual ice loss occurs through solid-ice discharge; in Antarctica such calving processes account for almost all ice loss. The resulting icebergs come in various sizes and shapes, some several hundred metres high. Immediately after they break off, when their height exceeds their horizontal extent, these floating giants can be unstable and capsize. In a paper in the *Annals of Glaciology*, MacAyeal and colleagues[1] have estimated the energy that is released when icebergs roll over. They find that this can be as large as that of an earthquake of magnitude 5–6 on the Gutenberg–Richter scale, depending on the iceberg's dimensions.

As one of several possibilities, a proportion of this energy can generate a surface gravity wave — a tsunami. MacAyeal *et al.* provide a theoretical analysis of the potential of iceberg capsize to generate tsunamis. Assuming a simplified, but not completely unrealistic, rectangular geometry, they calculate the potential energy before and after capsizing. The difference is the energy released from the roll-over. Thin icebergs do not carry a lot of potential energy, whereas ice-cube-shaped icebergs, which are as thick as they are high, have the same potential energy before and after turning over. Thus the most energy is released by icebergs that are half as thick as they are high — and can be equivalent to the explosion of several thousand tonnes of TNT.

According to MacAyeal and colleagues[1], energy release increases with the fourth power of an iceberg's height (Box 1). But not all of