of the effect of probiotics on plasma TMAO levels and on cardiovascular disease in humans would be of interest.

Because TMAO is produced in the liver by the action of the flavin monooxygenase FMO3, inhibition of this enzyme in the liver might be another strategy by which to reduce TMAO production and cut the risk of heart disease. Although complete absence of FMO3 — for instance, in the disease trimethylaminuria — is undesirable, its reduced activity might be beneficial. Whether variations in the gene encoding FMO3 that reduce its activity are associated with reduced plasma TMAO levels and, more importantly, with reduced incidence of cardiovascular disease, should be tested.

Although Wang and colleagues' work[1] suggests that excess dietary choline might lead to cardiovascular disease, choline is an essential nutrient for several cellular metabolic pathways. So any attempt to reduce the levels of choline or its metabolites for therapeutic purposes requires caution. Nonetheless, this study has added phosphatidylcholine and other sources of dietary choline — such as the widely used food supplements — to the list of dietary culprits with the potential to increase the risk of heart disease. What's more, it implicates the gut microbiome in promoting heart disease in the setting of a high-choline diet. The implications for prevention of cardiovascular disease are tangible, and the subsequent chapters in this story will make fascinating reading. ■

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ELECTRONICS

Industry-compatible graphene transistors

An innovative technique has been developed to manufacture graphene transistors that operate at radio frequencies and low temperatures. The process brings the devices closer to applications. SEE LETTER P.74

FRANK SCHWIERZ

To an increasing extent, modern society relies on advances in wireless communications. The backbone of wireless systems is radiofrequency (RF) transistors that are able to amplify signals and provide electronic gain at high frequencies. Unfortunately, these abilities degrade with increasing frequency, but emerging applications require ever higher operating frequencies. On page 74 of this issue, Wu *et al.*[1] describe transistors made from graphene — a carbon sheet just one atom thick — that hold promise for RF applications.

Two parameters are used to assess the frequency performance of an RF transistor: the cut-off frequency, f_T, at which the device's current gain drops to unity; and the maximum frequency of oscillation, f_{max}, at which the power gain becomes unity. One way to enhance the frequency performance of transistors is to use new materials that have high charge (carrier) mobility. The ultra-high mobilities observed[2,3] in graphene attracted the attention of device engineers immediately after their discovery, and intensive research[4,5] on RF graphene transistors is now under way.

Significant progress has been made since the demonstration[6] of the first gigahertz graphene transistors in 2008. Most notably, in February 2010, a group reported[7] a field-effect transistor (FET, the type of transistor most frequently used in electronics) made from graphene that broke the 100-GHz-f_T mark. And only a few months later, researchers demonstrated[8] a graphene FET that has an f_T of 300 GHz. Wu *et al.*[1] now report graphene FETs with gate electrodes of remarkably short length (40 nanometres) and f_T as high as 155 GHz. This result certainly does not represent a new record in frequency performance for RF transistors, and one might say that this is just another report on the good performance of graphene transistors. In fact, it is more than that in several respects.

Most groups make graphene by mechanical exfoliation, a method described[2] by Nobel prizewinners Konstantin Novoselov and Andre Geim. Mechanical exfoliation consists of peeling graphene flakes off a graphite crystal, and is a neat and practical method for university labs; the 300-GHz-f_T transistor mentioned above is made from exfoliated graphene. To make graphene attractive for the electronic-chip industry, however, reliable large-scale preparation schemes are needed. One such scheme, pioneered by Berger and de Heer[9], is the growth of graphene, by a method known as epitaxy, on silicon carbide wafers. A second option is to use a process known as chemical vapour deposition (CVD) to grow graphene on a metal, and then to transfer the graphene from the metal onto an insulating substrate, which most commonly consists of silicon with a top layer of silicon oxide (SiO_2)[10]. Wu and colleagues[1] now present a promising modification of the latter approach, which is to use a diamond-like carbon film as the top layer. Using this instead of SiO_2 is thought to result in better carrier transport in graphene FETs.

The authors[1] fabricated graphene transistors with gate lengths in the 40–550-nm range. They demonstrate reproducible measured characteristics for 30 devices and cut-off frequencies up to 155 GHz. Although this f_T value does not exceed that obtained previously[8], it is the highest f_T reported for CVD graphene transistors. Wu *et al.* also provide the first RF data for CVD graphene FETs on diamond-like carbon. With this work, another industry-compatible technology option for RF graphene FETs is now available.

What's more, Wu and colleagues are the first to investigate graphene FETs at very low temperatures. They show that the f_T of their transistors remains essentially constant between 300 kelvin and liquid-helium temperatures (4.2 kelvin), proving that graphene transistors could represent an alternative to conventional silicon- and III-V-semiconductor-based FETs for use at cryogenic temperatures, for example in space-based applications. It should be noted that proper operation of devices at 4.2 K is not a matter of course. There were serious concerns that carrier freeze-out might degrade the performance of silicon transistors of the MOSFET type at low temperatures. Fortunately, experiments[11] showed that this was not the case.

Finally, Wu and co-workers discuss not only the merits but also, and quite thoroughly, the problems of graphene transistors. The f_T performance of graphene FETs is known to be very competitive. For most applications, a high f_T is certainly desirable, but more important than a high f_T would be high power gain and f_{max}. Unfortunately, graphene FETs still suffer from low f_{max}. The 550-nm-gate graphene FETs of Wu *et al.* display an f_{max} of only 20 GHz. Although this is the highest f_{max} reported so far for graphene RF FETs, it is much lower than that of competing RF FETs (Fig. 1). Moreover, in

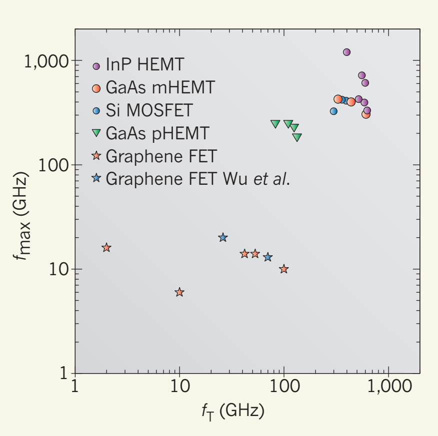

Figure 1 | Frequency performance of graphene transistors. Maximum frequency of oscillation, f_{max}, versus cut-off frequency, f_T, for graphene field-effect transistors (FETs) and competing radiofrequency FETs: indium phosphide high electron mobility transistor (InP HEMT), gallium arsenide metamorphic 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