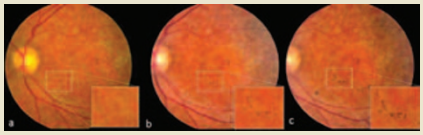
ES cell therapy in two patients with eye disease



Preliminary data from two ongoing trials that aim to assess the safety of transplantation of human embryonic stem cells (hESCs) into human eyes to treat blindness are encouraging, according to Schwartz *et al.* One trial is for age-related macular degeneration, the other is for Stargardts macular dystrophy (SMD). The researchers prepared differentiated hESC-derived retinal pigmented epithelial (RPE) cells and tested them preclinically by transplantation into rat retinas to ensure the hESC-RPEs were pure and did not form teratomas. The stage of hESC-RPE differentiation mattered: cells with less melanin engrafted more efficiently than those with more melanin and were judged suitable for testing in humans. Two patients (one from each trial; each trial will eventually enroll 12 patients) had 50,000 hESC-RPEs transplanted into a part of one retina where degeneration was incomplete. Outcomes measured included demonstration of successful engraftment of hESC-RPEs, but only in the patient with SMD. At 4 months after engraftment, neither patient had any adverse outcomes, such as hyperproliferation, transplant rejection or teratoma. Both phase 1/2 trials will also assess clinical endpoints, such as visual acuity, for future efficacy trials. The trials will be fully enrolled in 2012, but pivotal phase 3 trials will then be needed to evaluate whether hESC-RPEs can improve clinical outcomes. (*Lancet*, doi:10.1016/S0140-6736(12)60028-2, published online 24 January 2012) *SJ*

Turning seaweed into biofuel

Much of the dry biomass in seaweed is locked up in the form of sugars such as alginate, mannitol and glucan that most industrial microbes cannot metabolize. In a feat of genetic engineering, Wargacki *et al.* have succeeded in creating a strain of *Escherichia coli* capable of converting a large bulk of this sugar into the biofuel ethanol. Most of this inaccessible sugar is present as alginate, a linear copolymer of two uronic acids. To metabolize alginate into ethanol, the researchers expressed over 20 new genes from three different species (*Vibrio splendidus* 12B01, *Pseudoalteromonas* sp. A1 and *Agrobacterium tumefaciens*) in *E. coli* and deleted seven endogenous genes to ensure efficient fermentation into ethanol rather than other by-products. Using culture techniques that do not require any chemical, thermal or enzymatic pretreatments before fermentation, the authors achieved an ethanol titer of almost 5% volume/volume, reaching yields of over 80% of the maximum theoretical yield based on the sugar composition in seaweed. Seaweed is an especially attractive feedstock for biofuel production because its cultivation does not take valuable farmland away from other crops. (*Science* **335**, 308–313, 2012) *JK*

Engineering control in biofilms

Mixed communities of bacteria in a biofilm can perform multistep transformations that are important in bioremediation and microbial fuel cells, but typically biofilms have not been easy to engineer. Hong *et al.* report a microfluidic biofilm engineering circuit that is based on a population-responsive quorum-sensing switch. The basis of the system is a primary genetic switch that responds to a diffusible quorum-sensing signaling molecule together with a secondary switch that responds to a chemical inducer. Each of the two gene circuits includes previously identified genes that encode proteins engineered by the group to mediate enhanced biofilm dispersal. Different populations were labeled green (colonizers) and red (dispersers) using the respective fluorescent protein tags, allowing community dynamics to be tracked. A colonizer biofilm was established and overgrown with a disperser biofilm to form a dual-species community. Once this attained sufficient population density, synthesis of the diffusible signal by dispersers resulted in removal of at least 80% of the colonizer community. Subsequent exogenous addition of the chemical inducer removed 100% of the disperser community. The approach opens up the possibility of studies of the dynamics of biofilm formation and dispersal and of antibacterial activity on such structures. (*Nat. Comm.* **3**, doi:10.1038/ncomms1616, published online 3 January 2012) *SJ*

Written by Kathy Aschheim, Laura DeFrancesco, Susan Jones & Jason Kreisberg

Resveratrol mechanism revealed

The link between resveratrol (a polyphenol found in grapes) and longevity has been hotly pursued since it was found to activate Sirt1, a member of the sirtuin acetylases believed to be central in mediating the health benefits of caloric restriction. The actual linkages among these molecules and outcomes are still being sorted out, but at least now we have some idea of the mechanism whereby resveratrol exerts its influence, thanks to work by Park and colleagues. The researchers focused on energy metabolism, given its central role in aging, and on the finding that resveratrol activates Sirt1 via AMP-activated protein kinase (AMPK), an energy sensing enzyme. Through direct dissection of the pathways, they were able to pinpoint a set of phosphodiesterases (PDEs) as resveratrol's target and to identify the intermediates from the induction of cyclic AMP production (following PDE inhibition) to Sirt1 activation. Comparing the effects of the PDE inhibitor rolipram to resveratrol *in vivo* further established the identity of the target; in mice fed a high-fat diet, rolipram raised the transcription level of genes involved with mitochondrial biogenesis in skeletal muscle to levels as to those for resveratrol, suggesting that existing PDE inhibitors may be repurposed to treat age-related diseases. (*Cell* **148,** 421–433, 2012) *LD*

Reprogramming illuminates Alzheimer's

Research on Alzheimer's disease has been hampered by a lack of good disease models. Mice carrying mutations linked to familial Alzheimer's do not develop the full spectrum of aberrant phenotypes, and neurons from postmortem patients are not readily available. Israel *et al.* have now shown that patient-derived induced pluripotent stem cells provide an alternative way of modeling Alzheimer's. They found that neurons generated *in vitro* from fibroblasts of patients with either familial or sporadic disease reproduced important features of the pathology, including increased levels of amyloid-β_{1-40}, phospho-tau and active glycogen synthase kinase-3β (aGSK-3β). To begin to unravel the causal relationships between these three dysregulated proteins, the authors treated the neurons with inhibitors of β- or γ-secretases, which cleave the amyloid precursor protein into several products, including amyloid-β_{1-40}. These experiments revealed that processing of amyloid precursor protein induces phospho-tau and aGSK-3β. Because the neurons generated from one patient with sporadic disease resembled those from the familial-disease patients, the authors suggest that this case of sporadic disease is likely to have a previously unappreciated genetic basis. (*Nature* **482**, 216–20, 2012) *KA*