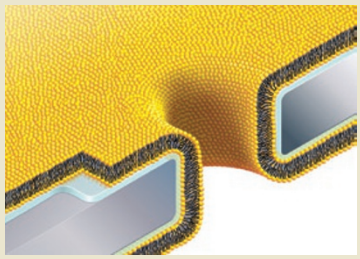
Lipid-coated nanopores



Artificial nanopores have received considerable attention as detectors of single proteins and small molecules, and for high-speed DNA and RNA sequencing. However, low molecular specificity and difficulties in detecting molecules at high translocation speeds have limited their application. Now, Yusko *et al.* suggest that coating synthetic nanopores with fluid lipid bilayers can help to overcome these problems. Inspired by similar structures in the olfactory system of insects, the authors exposed a silicon nitride matrix with 20–30 nm pores to a suspension of liposomes and showed that the lipids form a bilayer on the silicon nitride surface. Biotinylated lipids acted as specific receptors for target molecules, increasing their concentration on the nanopore surface. When an electric field was applied over the nanopore membrane, the fluid character of the bilayer allowed the biotin-bound molecules to translocate through the nanopores, enabling their detection by a characteristic change in the conductance. The high viscosity of the lipid bilayer reduced the translocation speed to permit detection. In addition to offering a potential solution to the selectivity and sensitivity problem, lipid-coated pores were much less prone to clogging caused by unspecific adsorption of protein to the pore. (*Nat. Nanotechnol.* **6**, 253–260, 2011) *ME*

Turning mouse tails into liver

Liver transplantation is the only remedy for liver failure, but many people in need of a transplant die awaiting a donor. Whereas stem cells of various kinds can be coaxed to form hepatocytes, the protocols are involved and inefficient. Now Huang *et al.* show that with three transcription factors, immortalized mouse tail tip fibroblasts can be coaxed to transdifferentiate into cells functionally equivalent to hepatocytes (iHep cells). Starting with 14 transcription factors that are important for liver development, the researchers pared it down to three—Gata4, Hnflα and Foxa3. The iHep cells displayed various hepatocyte characteristics *in vitro*, such as forming tight junctions and expressing E-cadherin. Global gene expression in iHep cells clustered with hepatocyte expression patterns rather than fibroblast patterns. In a mouse model for liver failure, injecting iHep cells into the spleen rescued almost half (5/12) of treated animals, whereas all untreated animals (10/10) died. In the surviving mice, iHep cells made up 5–80% of the liver and the functional hepatocytes were clearly not fusions of transplant and host cells, as shown by chromosome analysis (female iHep cells were transplanted into male recipients). Importantly, because the cells had been immortalized, there was no sign of tumors when iHep cells were transplanted either into the mice prone to liver failure, even several months later, or into nude mice. This promising approach will need to be done with human cells before its therapeutic potential will be known. (*Nature* published online, doi:10.1038/nature10116, 11 May 2011) *LD*

Written by Kathy Aschheim, Laura DeFrancesco, Markus Elsner, Peter Hare & Craig Mak

Unearthing microbiome secrets

Just as human physiology is influenced by microbial communities in our gut and skin, the tolerance of plants to root diseases depends on the microbial flora in the soil, according to a new report by Mendes *et al.* The researchers studied disease-suppressive soils that confer protection against the fungal pathogen *Rhizoctonia solani*, which afflicts crops, including sugar beet, potato and rice. Mendes *et al.* used a high-density microarray of 16S ribosomal-DNA oligonucleotides to compare the microbial content of different soils, finding several bacterial taxa associated with disease suppression. Follow-on work in culture pinpointed a strain of bacteria capable of protecting sugar beet seedlings from *R. solani*. And subsequent transposon mutagenesis of this strain identified a nonribosomal peptide synthetase gene that was required for the bacteria to protect the plants. The gene is part of a pathway predicted to produce a nine-amino-acid chlorinated lipopeptide. This work highlights the potentially complex relationships between plants and the soil microbiome and raises the intriguing possibility of harnessing these relationships for agricultural benefit. (*Science* published online, doi:10.1126/science.1203980, 5 May 2011) *CM*

SRC and trastuzumab resistance

Trastuzumab (Herceptin), a humanized antibody that targets epidermal growth factor receptor 2, is indicated for adjuvant treatment of HER2-overexpressing node-positive or node-negative breast cancer. Many breast cancer patients are, however, unresponsive to initial treatment, and others frequently develop resistance to trastuzumab over time, spurring efforts to identify mechanisms of resistance. Zhang *et al.* now show that the hyperactivated tyrosine kinase c-SRC is a common node downstream of multiple *de novo* and acquired trastuzumab-resistance pathways. Increased c-SRC activation correlated with poorer responses to trastuzumab in patients and conferred resistance to the drug in cultured cells. Most notably, an orally available, small-molecule c-SRC inhibitor sensitized five different classes of trastuzumab-resistant cells to the antibody and enabled trastuzumab-mediated elimination of drug-resistant tumors in a mouse xenograft model. These findings suggest that a combinatorial regimen of c-SRC inhibitor with trastuzumab may be a practical way to overcome multiple modes of trastuzumab resistance in the clinic. (*Nat. Med.* **17**, 461–469, 2011) *PH*

iPSCs shed light on schizophrenia

Modeling a disease with induced pluripotent stem cells (iPSCs) involves reprogramming somatic cells from a patient, differentiating the iPSCs to a cell type that is affected in the disease and showing that the differentiated cells exhibit essential features of the pathology. This last step—recovering the disease phenotype—is usually the hardest, and the most compelling examples to date have come for monogenic diseases that occur in childhood. A recent paper reports progress in using iPSCs to model a multigenic disease that strikes most often in adolescence. Brennand *et al.* found that iPSC-derived neurons from individuals with schizophrenia reproduced certain aspects of the disease seen previously in animal models or in human post-mortem neurons (e.g., a reduction in neuronal connectivity and neurite number). However, other known characteristics of the disease were not detected (e.g., impaired synaptic function). Transcriptional profiling of the disease-specific and normal neurons showed 596 differentially expressed genes, 25% of which have been linked to schizophrenia. iPSCs derived from patients offer a new approach for drug testing; the authors found that one of five antipsychotic drugs studied mitigated the disease phenotype *in vitro*. (*Nature* **473**, 223–225, 2011) *KA*