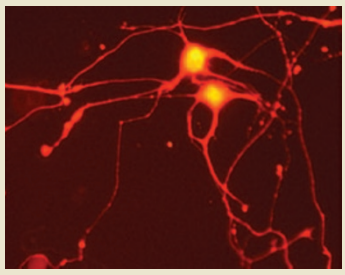
Hepatocytes go neuronal



Fibroblasts, both human and mouse, can be directly converted into neurons by adding the three transcription factors Ascl1, Brn2 and Myt1l. This suggests that cells can transdifferentiate without going through an embryonic phase. However, because fibroblast preparations contain some neural stem cells, among others, it isn't clear which cell type transdifferentiates. Marro *et al*. show definitively that terminally differentiated cells transdifferentiate. Using the same three transcription factors, they convert a homogeneous population of hepatocytes into cells with neuronal morphology and properties (Hep-iN cells). Hep-iN expression profiles resemble neuronal patterns more than hepatocyte patterns; of a set of genes with known function in liver, all of them were downregulated in Hep-iN cells, as were 85% of 149 genes preferentially expressed in liver. These results show that the same factors can downregulate both fibroblast-specific and hepatocyte-specific genes. Furthermore, the authors demonstrate that any cell type, even ones that derive from germ layers besides the ectodermal germ layer (which gives rise to neurons), can transdifferentiate into neurons. (*Cell Stem Cell* **9**, 372–382, 2011) *LD*

Antibody clamps phosphatase inactive

Over the past two decades, the phosphatase PTP1B has been found to be a key regulator of signaling pathways triggered by the hormones insulin and leptin. Yet efforts to discover small molecules to treat diabetes and obesity by targeting the active site of PTP1B have thus far failed to produce candidates suitable for use as drugs. Using phage display and a mutant version of PTP1B that mimics the enzyme in its inactive oxidized conformation, Haque *et al.* isolated a single-chain variable fragment antibody (scFv) that stabilizes the inactive form of PTP1B, thereby inhibiting phosphatase activity. The scFv is functional in 293T cells, where it enhances cellular responses to insulin, as measured by phosphorylation of both insulin receptor and AKT, which is a downstream readout of the pathway. Moreover, data suggest that the scFv is specific to PTP1B and does not inhibit a closely related phosphatase. These results could spur efforts toward developing small-molecule drugs that mimic the conformation-stabilizing effects of the scFv. (*Cell* **147**, 185–198, 2011) *CM*

Nanopores quantify miRNAs

Building on an approach published last year by Wanunu *et al.* using nanopores to quantify the concentration of microRNAs (miRNAs), Wang *et al.* now create a clinical diagnostic test for circulating cancer-associated miRNAs. This assay exploits the transient reduction of an electrical current through a nanopore when a charged polymer is threaded through the pore. To identify specific miRNAs, complementary probes are hybridized to purified RNAs. The probe:miRNA complexes show drastically different translocation kinetics from free miRNA. For quantification of the miRNA concentration, translocation events per unit time are counted and compared with a standard curve. In contrast to Wanunu *et al.*, who use an artificial nanopore, Wang *et al.* employ the α-hemolysin protein pore of *Staphylococcus aureus* and show that the nanopore can be used with patient-derived samples to quantify diagnostically relevant circulating miRNAs. Wang *et al.* also show that they can detect miRNAs at subpicomolar concentrations and that they can accurately distinguish single nucleotide differences between related RNAs. (*Nat. Nanotechnol.* **5**, 807–814, 2010; *Nat. Nanotechnol.* **6**, 668–674, 2011) *ME*

Sequencing translocations

Although large-scale structural variations and chromosomal translocations are common in many cancers, relatively little is known about molecular mechanisms that cause genome rearrangements. Translocations are thought to begin with a double-stranded break in two chromosomes. In two recent papers, Chiarle *et al.* and Klein *et al.* investigated what genomic translocations occur when an experimentally introduced double-stranded break is repaired by an immune cell. Both groups studied B lymphocytes and used a specific meganuclease to cause breaks in either the *c-myc* gene or the *IgH* locus (an *IgH*/*c-myc* translocation is involved in the genesis of many B-cell lymphomas). DNA libraries enriched for rearrangements were sequenced by high-throughput sequencing. The authors found a wide spectrum of translocations involving all chromosomes. The analysis of hundreds of thousands of individual events in wild-type primary cells showed that the translocation sites are not randomly distributed in the genome, but that a small number of hotspots exist. The majority of translocations are within active genes, mostly around the transcriptional start site. The activation-induced cytidine deaminase (AID), a protein involved in IgH class switch recombination and somatic hypermutation, also contributes to the genesis of translocations by initiating double-stranded DNA breaks, as many hotspots observed in wild-type cells disappear when AID knockout cells are analyzed. (*Cell* **147**, 95–106, 2011; *Cell* **147**, 107–119, 2011) *ME*

Toward human therapeutic cloning

A recent paper by Noggle *et al.* reports an advance in human somatic cell nuclear transfer (SCNT). The ability to produce human pluripotent stem cells by transferring a somatic-cell nucleus into an enucleated oocyte would provide another way of generating patient-specific stem cells in addition to methods for converting somatic cells to induced pluripotent stem cells. (For a comparison of the two reprogramming strategies, see *Nat. Biotechnol.* **29**, 701–705, 2011). Stem cell lines have been derived through SCNT for several mammalian species but not yet for human. In part, this can be explained by the scarcity of human oocytes available for research, but it's also possible that human cells are intrinsically more resistant to SCNT. Noggle *et al.* show that the tendency of human SCNT embryos to arrest at an early stage of development can be overcome if the oocyte nucleus is left in place rather than removed, allowing derivation of triploid stem cells. This suggests that the human nucleus provides unknown, essential factors that, once identified, could permit the generation of normal diploid stem cells. (*Nature* **478**, 70–75, 2011) *KA*

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