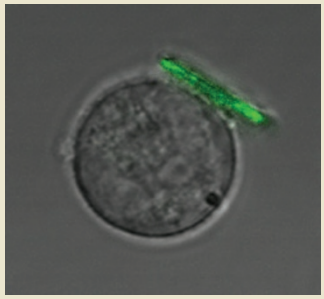
Put a patch on it



Imagine being able to patch new functions onto cells simply by refashioning parts of their surfaces. Swiston *et al.* have achieved just that, devising a payload-bearing patch that attaches to part of the surface of lymphocytes, leaving most of their remaining membrane surface free and functional. The patch is multilayered, consisting of a patterned polymer film formed photolithographically from poly(methyacrylic acid and poly (*N*-isopropylacrylamide); a payload layer of paramagnetic nanoparticles and fluorescein isothiocyanate-labeled poly(allylamine hydrochloride); and a cell adhesive layer consisting of hyaluronic acid/chitosan, which binds CD44 receptors. Once adhered to the film surface, cells are detachable under nontoxic conditions (temperature or pH). Patch-bearing lymphocytes were viable for 72 hours by virtue of their payload; they could be manipulated using a magnetic field while retaining normal function; they were able to migrate across a field of the intercellular adhesion molecule (ICAM)-1, which binds to integrin on T cells. Cells could be fashioned into rings or sheets or could pick up more than one patch according to the structure of the film and the dimension of the patch. This represents the first demonstration of an environment-sensing patch that leaves normal cell function intact. It may enable immune cells to deliver drugs or imaging agents, as well as provide insights into membrane dynamics. (*Nano Lett.*, published online 5 November 2008 (doi:10.1021/nl802404h)) *LD*

Integrated tumor suppressor screening

With the discovery of myriad mutations and chromosomal aberrations in cancer cells, the problem becomes identifying those that contribute to the cancer phenotype—as opposed to 'passenger' mutations in unstable genomes. Knockout mice have been used to determine the function of putative tumor suppressors or oncogenes, but the technique is costly and time consuming. Zender *et al.* now describe a mouse mosaic model system for validating suspected tumor suppressor genes. The researchers screened 100 human hepatocarcinomas for deletions, reasoning that deleted regions harbor tumor suppressors. Within 58 deletions, they identified 362 genes, 301 of which had mouse orthologs. They then used short hairpin RNAs (shRNAs) to target these mouse genes in previously generated immortalized lines of embryonic hepatocytes that lack p53 and overexpress Myc and thus have a heightened propensity for tumorigenesis. Most hepatoblasts so transfected produced tumors, whereas those transfected with random shRNAs did not. To pinpoint shRNAs targeting tumor suppressors, rather than passenger mutations, they isolated those highly enriched in tumors and repeated the exercise with individual shRNAs. Among the genes whose silencing stimulated tumorigenesis were 12 that encoded previously unidentified tumor suppressors, several of which are secreted proteins, making them potential targets for therapeutics. In addition, several suppressors were present in deletions found in human breast cancer, suggesting a broader role in other tumor types. (*Cell*, published online 13 November 2008 (doi 10.1016/j.cell.2008.09.061)) *LD*

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

Potentiating siRNA therapy in cancer

A propensity to activate the type I interferon response has long been regarded as a disadvantage of short interfering RNA (siRNA) therapeutics modified with 5′ triphosphate groups. But a collaboration of investigators from academia and industry has turned this broad immune priming effect to their advantage when designing an siRNA therapy for use in a mouse model of lung metastases. Poeck *et al.* create an siRNA molecule modified with a triphosphate group at the 5′ end that targets a short region of the tumor survival factor Bcl2. When delivered to melanoma cells in the lungs of mice, this siRNA not only targets Bcl2 for sequence-specific degradation via the RNA interference pathway but also triggers an innate immune response via the 5′ triphosphate moiety, thereby potentiating tumor cell death. The authors demonstrate that their 5′ triphosphate RNA is more potent against melanoma cells than siRNAs lacking the triphosphate group. Their paper raises the possibility that 5′-triphosphate siRNA has greater potency in anticancer therapy, particularly in situations where broad activation of innate immunity can be localized, such as in delivery to the lungs. (*Nat. Med.*, **14**, 1256–1263, 2008) *CM*

Tissue-selective motifs predict miRNAs

Computational strategies to predict microRNAs (miRNAs) on the basis of their conservation between species are likely to miss miRNAs that emerged relatively recently in evolutionary time and might even be specific to the organism of interest. Taking advantage of features previously associated with miRNA genes, Chang *et al.* address this deficiency by first using expressed sequence tag (EST) data to define genes expressed in <6 of 40 human tissues and then using microarray data to eliminate highly expressed genes from the tissue-selective gene set. Computational analysis of the 3′ untranslated regions of the latter to identify overrepresented seven-nucleotide motifs identifies >66% of known human miRNAs and predicts the existence of 36 novel miRNA genes. Functional validation of two of these confirmed their targets to be cAMP-responsive element binding protein 3-like 3 and laminin β3. This approach promises to complement current strategies, the predictive potentials of which may be nearing saturation. (*Proc. Natl. Acad. Sci. USA* **105**, 17061–17066, 2008) *PH*

Keeping diabetes AAT bay

The link between diabetes and inflammation has attracted increased attention of late. In 2005, Dinarello and colleagues reported that immune rejection of transplanted allogeneic islets in mice with streptozotocin-induced diabetes could be delayed by treatment with the anti-inflammatory agent human α1-antitrypsin (hAAT). Two new studies further explore the potential of hAAT in diabetes therapy. A follow-up paper from the Dinarello group shows that hAAT monotherapy for 14 days in diabetic, hAAT-transgenic mice (which enable longer exposure to injected hAAT owing to the absence of anti-hAAT antibodies) leads to long-term allograft survival and normoglycemia. The authors demonstrate induction of tolerance to the allograft for up to 120 treatment-free days. In a related study, Koulmanda *et al.* investigate the effects of hAAT in non-obese diabetic (NOD) mice. Like humans with type 1 diabetes, NOD mice undergo autoimmune destruction of insulin-producing β cells. The authors show that treatment of overtly diabetic NOD mice with hAAT for 15 days results in enhanced immune tolerance to β cells, reduced insulitis, increased β-cell mass and long-lasting normoglycemia. Both papers provide evidence that tolerance to β cells can be induced by modulating the inflammatory milieu, which influences the balance between effector and regulatory T cells. (*Proc. Natl. Acad. Sci. USA* **105**, 16242–16247, 2008; *Proc. Natl. Acad. Sci. USA* **105**, 16236–16241, 2008) *KA*