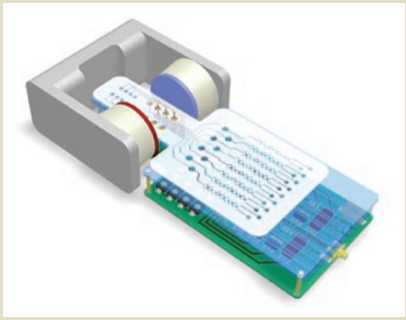
NMR on a chip



Advances in miniaturizing NMR reported by Ralph Weissleder and his colleagues bring point-of-care devices for detecting disease markers one step closer to the bedside. Combining microfabrication techniques with molecular proximity assays, the group describes a handheld multi-channel NMR device that can perform proton T_2 measurements on microliter quantities of complex fluids at a minimum of 80-fold greater sensitivity than a benchtop relaxometer. The device contains an array of microcoils on a glass wafer, over which is mounted a microfluidics network, for sampling handling and distribution. One key to success is the use of magnetic nanoparticles coated with affinity ligands, which self-aggregate, thereby amplifying the signal. With this system, the authors can detect as few as ten bacteria in 15 minutes using vancomycin-coated nanoparticles—existing approaches that identify pathogens by DNA probes or growth in culture take hours to days—and single macrophages, which take up the nanoparticles by phagocytosis. What's more, they quantify multiple biomarkers on cancer cell surfaces using nanoparticles derivatized with monoclonal antibodies (cetuximab (Erbitux) for epidermal growth factor receptor and trastuzumab (Herceptin) for Her2/neu). Finally, using a 2×4 microcoil array, they detect eight different biomarkers and distinguish samples concocted to resemble ones from diabetes patients from those that resemble samples from cancer patients. (*Nat. Med.* advance online publication, 6 July 2008 (doi: 10.1038/nm.1711)) *LD*

Containing live vaccines

Live-attenuated pathogens used in vaccine production pose an environmental risk; thus far, attempts to permanently disable vaccine strains have been inadequate. To address this problem, Roy Curtiss and his colleagues engineer a strain of *Salmonella typhimurium* to undergo programmed lysis after entering a host—with a view to not only hobble the bacteria's ability to reproduce but also potentiate antigen delivery. They hypothesize that by causing cell lysis and the release of intracellular antigens, vaccine efficacy might be improved to the point that the developing world can afford them. They set out to accomplish this by first engineering a strain to have arabinose-dependent expression of two genes essential for cell wall synthesis. To achieve absolute arabinose dependency, they substitute some control elements to get tight control of expression and introduce an antisense-generating system for mopping up any residual transcripts. The resulting strain grows in arabinose-containing medium but dies within an hour of arabinose removal. In mice, a strain engineered to deliver a fusion of β-lactamase and pneumococcal surface protein A gene from *Streptococcus pneumoniae,* a particular problem in the developing world, induces a robust immune response with no viable vaccine remaining after 21 days. The authors point out that this biological containment system could have other uses beyond antigen delivery. (*Proc. Natl. Acad. Sci.* **105**, 9361–9366, 2008) *LD*

Written by Kathy Aschheim, Laura DeFrancesco & Peter Hare

New uses for approved drugs

A paper by Peer Bork and colleagues exploits data about the side effects associated with 746 marketed drugs to predict unanticipated drug targets of therapeutic interest. Their side-effect-similarity measure identifies 261 pairs of chemically dissimilar drugs. When 20 of these unexpected relationships are tested experimentally, 13 of the drugs approved for one indication are shown to bind a target of their structurally disparate partner *in vitro*. In all nine of these instances where a cell assay was available, the predicted cellular activity was confirmed and the K_i values of seven of the novel interactions are within an order of magnitude of the average drug concentrations in the plasma. The approach promises to suggest new leads for drug development, and potentially decrease the time and expense associated with regulatory approval. (*Science* **321**, 263–266, 2008) *PH*

Deciphering reprogramming

What occurs inside a differentiated cell during the 10 or more days required to reprogram it to an induced pluripotent stem (iPS) cell? A deeper understanding of the reprogramming process could guide research aimed at improving this nascent technology. To this end, Tarjei Mikkelsen *et al.* study global gene expression, histone methylation and DNA methylation in cells that are partially or fully reprogrammed by ectopic expression of *Oct4*, *Sox2*, *Klf4* and *c-Myc*. Global gene expression profiling through day 16 of mouse embryonic fibroblasts (MEFs) undergoing reprogramming reveals early downregulation of mesenchymal genes expressed in MEFs and upregulation of genes associated with proliferation, stress and anti-proliferation, and later upregulation of genes associated with differentiating MEFs. The authors note that some of these changes "may prevent the majority of cells from reaching a stably de-differentiated state." Gene expression and epigenetic profiling of fully reprogrammed iPS cells shows that these cells turn on genes associated with pluripotency and self-renewal, establish an open chromatin state and silence lineage-specifying genes. These processes are found to be incomplete in three cell lines arrested at intermediate stages of reprogramming. (*Nature* **454**, 49–55, 2008) *KA*

Adult stem cells muscle up

Cerletti *et al.* show that engraftment of skeletal muscle with a subset of adult satellite cells characterized by five cell-surface markers reconstitutes myofiber formation more effectively than previously investigated myogenic cell populations. Using an immunocompetent mouse model of Duchenne muscular dystrophy, they demonstrate that the engrafted skeletal muscle precursor cells contribute to up to 94% of myofibers, improving muscle contractility, restoring expression of normal dystrophin and reducing muscle inflammation and fibrosis. Besides these short-term reparative effects, the transplanted cells effectively repopulate the satellite cell niche, making them available for subsequent regenerative myogenesis. Better characterization of this readily available and transplantable stem cell–type, which normally contributes to muscle growth and repair, may open the way for other therapies to remedy muscle degeneration. (*Cell* **134**, 37–47, 2008) *PH*