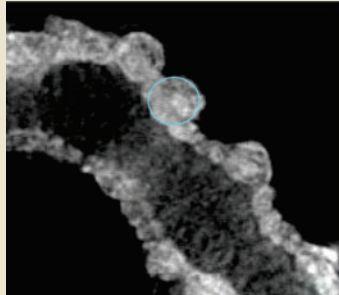


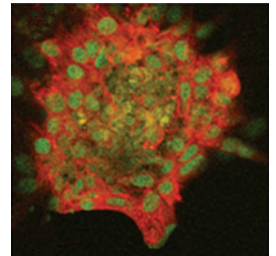
Ion-channel inhibitors on demand

Xu *et al.* describe a simple approach to producing polyclonal antibodies that can be used to effectively inhibit ion channels. The strategy consists of generating ion-channel inhibitory antibodies by targeting the third extracellular region (E3) of typical six-transmembrane-domain channels, such as the voltage-gated sodium, calcium and potassium channels as well as members of the transient receptor potential (TRP) calcium channel family. The authors test the concept by raising a specific TRPC5 inhibitor, which allows them to explore TRPC5 function in a previously intractable physiological system, and developing an antibody to the voltage-gated sodium channel $\text{Na}_v1.5$, which acts as a subtype-specific inhibitor. This approach holds promise as a systematic means of producing specific ion-channel inhibitors that could be exploited in therapeutics or for experimental purposes in routine assays on cells or tissues from a range of species. [Articles, p. 1289; News and Views, p. 1234] GTO



β -cells attain immortality

A promising alternative to insulin injections, transplantation of pancreatic β -cells may one day provide a cure for type 1 diabetes. For the moment, however, development of this therapy is hampered by a severe shortage of donor, cadaveric islets. One possible solution is to immortalize and expand mature human β -cells, but so far this strategy has not succeeded as the cells tend to senesce or lose β -cell function. Narushima *et al.* report the generation of an expandable, functional human β -cell line that may be suitable for transplantation. The reversibly immortalized cell line was made by transducing primary β -cells with retroviruses bearing the immortalizing genes *SV40T* and *TERT* (encoding the simian virus 40 large T antigen and human telomerase reverse transcriptase, respectively), flanked by loxP sites for later excision by Cre recombinase. The authors assayed over 250 transformed cell lines for lack of tumorigenicity and production of five β -cell-associated proteins, including insulin. Only one cell line, NAKT-15, passed this test. NAKT-15 cells were expanded and then 'reverted' by Cre expression to remove tumorigenic potential and promote recovery of β -cell function. Additional screening steps eliminated any cells that continued to express *SV40T* or *TERT*. *In vitro* experiments showed that the resulting cells mimic primary human β -cells in many respects, although insulin production is only ~40% of normal levels. When transplanted into diabetic mice, the cells controlled blood glucose levels for over 30 weeks. [Articles, p. 1274; News and Views, p. 1231] KA



Blueprint for bioremediation

Dehalococcoides species frequently populate contaminated groundwater, where they detoxify chlorinated organic compounds that might otherwise persist for decades. Adrian and colleagues report the complete genome of *Dehalococcoides* strain CBDB1. Analysis of the sequence not only provides insight into the propensity of *Dehalococcoides* spp. to dehalogenate xenobiotic compounds, but also suggests that intense evolutionary pressure has driven considerable diversification of reductive dehalogenase functions in these anaerobes. This is particularly evident in the extreme plasticity of clusters of genes that encode reductive-dehalogenase-homologous (*rdh*) genes. At less than 1.4 Mb, the *Dehalococcoides* strain CBDB1 genome is among the most streamlined of free-living prokaryotes. Nonetheless, strain CBDB1 contains a staggering 32 *rdh* genes—almost twice as many as in *Dehalococcoides* strain 195, the only other *Dehalococcoides* strain for which a complete genome is available. Accordingly, the two strains have different dechlorination spectra. Besides providing exceptional opportunities to study adaptation to anthropogenic pollution, *Dehalococcoides* genomics will likely pay valuable dividends in the restoration of environments polluted with chlorinated waste. [Articles, p. 1269; News and Views, p. 1236] PH

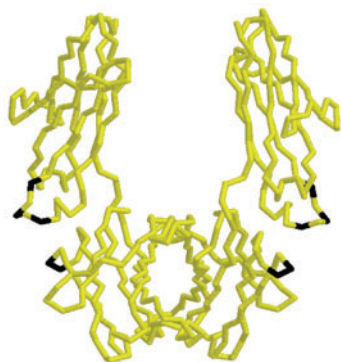
Diagnostics at the femtoscale

An ideal technology for detecting biomarkers would have ultrahigh sensitivity and selectivity, give a rapid, reproducible readout, avoid time-consuming preparation or labeling of the sample and permit multiple analytes to be identified simultaneously. Lieber and colleagues come close to this goal with an electrical sensor chip made of an array of silicon-nanowire field-effect devices. The fabrication method allows each of the more than 100 individually addressable positions on the array to display a particular type of nanowire (n-type, having electrons as charge carriers, or p-type, having holes as charge carriers) coupled to a particular antibody. When a protein binds the antibody, the device's conductance changes, a process similar to applying a voltage to the gate electrode of a field-effect transistor. For example, binding of a positively charged protein to a p-type device depletes charge carriers and decreases the conductance. The authors demonstrate selective, multiplexed detection of several purified cancer biomarkers, including prostate specific antigen (PSA), at low femtomolar concentrations. They also show selective detection of PSA at 0.9 pg/ml in undiluted serum containing 59 mg/ml protein. These results exceed the reported sensitivities of protein sensors based on carbon nanotubes, ELISA, surface plasmon resonance and microcantilevers. [Articles, p. 1294] KA

In This Issue written by Kathy Aschheim, Nadia Cervoni, Laura DeFrancesco, Michael Francisco, Peter Hare & Gaspar Taroncher-Oldenburg.

New IgGs on the block

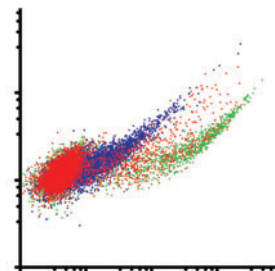
Manipulating the interaction between immunoglobulin G (IgG) protein and one of its receptors, FcRn, has long been used as a strategy to improve the pharmacokinetics of therapeutic antibodies. However, IgG stability is not always a welcomed event as in the case of autoimmune conditions, such as rheumatoid arthritis and systemic lupus erythematosus, where endogenous IgGs can prove deleterious. Ward and colleagues have introduced a new twist to the IgG engineering arena by creating a variant that binds to FcRn receptors with greater affinity than its endogenous counterparts. IgGs bound to FcRn are protected from degradation whereas unbound IgGs become subject to lysosomal degradation and clearance. Ward and colleagues demonstrated that their IgG variants could block the interaction between endogenous IgG and FcRn, resulting in improved degradation of endogenous IgGs *in vitro* and more rapid clearance of endogenous IgGs in a mouse model, as compared with controls. This approach may prove to be an important first step in developing therapeutics to treat antibody-mediated disorders. [Articles, p. 1283; News and Views, p. 1232] NC



one small molecule shown to inhibit cancer cell proliferation by 60%. This study demonstrates the potential for using protein-reactive small-molecule libraries for the discovery of drug targets and for providing insight into the mechanism of action of small-molecule probes. [Letters, p. 1303] NC

Tags that bind biarsenylated dyes

Although the small size and membrane permeability of biarsenylated fluorescein (FAsH) and resorufin (ReAsH) makes them powerful *in vivo* imaging agents, high levels of background fluorescence associated with their use remain a significant drawback. One way to tackle this problem is to optimize the sequence of the tetracysteine tag fused to the protein of interest that causes FAsH and ReAsH to fluoresce. Using fluorescence-activated cell sorting to screen a cell library containing different tetracysteine-tagged green fluorescent proteins (GFPs), Tsien and colleagues identify cells containing GFP tags with the highest fluorescence resonance energy transfer (FRET) to the biarsenical dyes. Several tag sequences with very stable FAsH and ReAsH complexes are identified with high fluorescence quantum yields. The >20-fold increase in labeling contrast thus achieved should be of interest to researchers using FAsH and ReAsH for fluorescent labeling *in vivo*. [Letters, p. 1308] GTO



Stuck on small molecules

High-throughput cellular screens of small-molecule libraries have been a mainstay of pharmaceutical discovery; however, because such screens often only assess drug activity on the basis of a functional assay, they cannot provide information on a compound's molecular mechanism of action. Cravatt and colleagues have created small-molecule compound libraries that bind covalently to their protein targets, enabling rapid and efficient target identification. Their starting point was a 50-member probe library that incorporates protein-reactive elements like those found in natural products; this was screened for antiproliferative activity against an invasive human breast cancer cell line, MDA-MB-231. By comparing *in situ* proteome reactivity profiles of library members, the authors identified an enzyme involved in glycolysis and recently found to be associated with cancer cell proliferation as the protein target of

Matrix reloaded

Although antibodies are commonly envisaged as the most potent affinity reagents because of their natural diversity and selectivity, they have their limitations. Because of their complex structure and large size, manufacturing antibodies for laboratory or clinical use is difficult and costly. But other binding molecules exist in nature, both structurally similar to antibodies and not. These structures provide scaffolds for creating binding molecules, using some of the same principles that have worked well for antibody engineering. Plückthun *et al.* detail what some of those nonantibody binders are, how they can be applied in areas from diagnostics to therapeutics and what technologies have been developed for creating and selecting scaffolds with specific properties. [Review, p. 1257] LD

Patent roundup

Are expressed sequence tags patentable in the United States? According to Davis and colleagues, the Federal Circuit's recent decision in *In re Fisher* may have decided the question once and for all. [Patent Article, p. 1227] MF
Recent patent applications in imaging technology. [New Patents, p. 1230] MF

Next month in

nature biotechnology

- Clinical data on superparamagnetic iron oxide-labeled dendritic cells
- Omega-3 pigs
- Fluorescent insect sexing
- Trans-splicing adeno-associated viral vectors
- RNA switches and Boolean logic