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In This Issue

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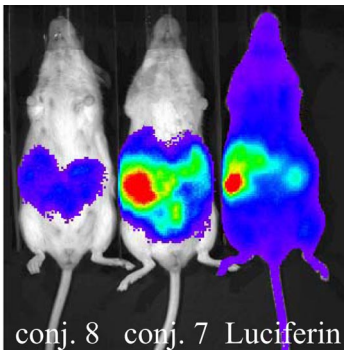
CHEMISTRY

Smuggling Taxol into cancer cells

Some cancer cells evade chemotherapy by expressing cell membrane pumps to expel toxins. One such pump is the P-glycoprotein, which exports the widely used chemotherapy compound Taxol as it passes through the membrane. To counter P-glycoprotein efflux, Elena Dubikovskaya *et al.* modified Taxol's structure, attaching a peptide that alters the mechanism by which the compound enters cells. The new conjugate, with different physical properties, is not a substrate for the pump. The authors attached the cell-penetrating peptide octaarginine to either the C2′ or C7 position in Taxol by using a disulfide bridge, which made the compound water-soluble (eliminating the need to use a noxious vehicle) and enabled the drug to cross the cell membrane without conventional diffusion. Outside the cell, the compound is inactive, but the reducing environment inside the cell cleaves the disulfide bridge, setting Taxol free. The authors demonstrated increased lethality of the conjugate compound in Taxol-resistant cell lines. Delivered by injection, both versions of the conjugate were more effective than Taxol against resistant tumors in mice. The method also ensures sustained drug release, rather than the "bolus" effect seen with conventional treatment, the authors say. — K.M.



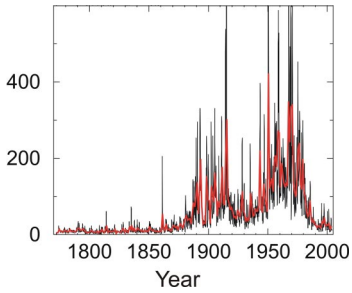
Effect of octaarginine (conj. 7) conjugation on drug biodistribution.

"Overcoming multidrug resistance of small-molecule therapeutics through conjugation with releasable octaarginine transporters" by Elena A. Dubikovskaya, Steve H. Thorne, Thomas H. Pillow, Christopher H. Contag, and Paul A. Wender (see pages 12128–12133)

ENVIRONMENTAL SCIENCES, SUSTAINABILITY SCIENCE

Coal's toxic legacy in the Arctic

Contemporary heavy metal pollutants from midlatitude industrial emissions travel through the atmosphere to colder Arctic climes, where they are deposited and bioconcentrated by plants and animals up the food chain. Little is known, however, about heavy metal pollution levels in the Arctic prior to 1980. Joseph McConnell and Ross Edwards measured concentrations of highly toxic thallium, cadmium, and lead in a Greenland ice core, constructing a month-by-month picture of pollution over the past two centuries, ending in 2003. Their evidence shows that until 1860, the metals existed at trace background levels and largely resulted from continental dust, forest fires, and volcanic activity. All three heavy metals began to accumulate during the late 1800s, with levels peaking in the 1910s and 1920s, crashing during the Great Depression, rising again during World War II, and falling after passage of the Clean Air Act enacted by the U.S. Environmental Protection Agency in 1970. Thallium and cadmium concentrations have since returned to near-preindustrial levels. Lead, which dropped by ≈90% after the phaseout of leaded gasoline and reductions in industrial emissions in the 1970s, is now 2.5 times greater than preindustrial levels. Coal burning appears to have been the main culprit for toxic heavy metal pollution a century ago, the authors say. — C.E.



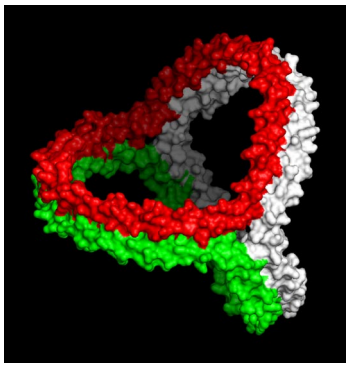
Monthly (black) and annual (red) lead concentrations (in pg/g) in central Greenland from 1772 to 2003.

"Coal burning leaves toxic heavy metal legacy in the Arctic" by Joseph R. McConnell and Ross Edwards (see pages 12140–12144)

BIOCHEMISTRY

Apolipoproteins bend in good cholesterol

High-density lipoproteins (HDLs) transport lipids and cholesterol in the bloodstream to the liver, where they are broken down. Levels of this "good cholesterol" inversely correlate with cardiovascular disease, the underlying cause of diabetes and many heart ailments. HDLs exist primarily in two forms in human plasma: spheres and discs. The sphere structure predominates *in vivo*, although the disc shape has been better characterized. Gangani Silva *et al.* studied the structure of apolipoprotein (apo) A-I in spherical HDLs. An α-helical polypeptide that makes up ≈70% of HDL protein mass, this apolipoprotein is the "glue" that holds HDLs together. Using cross-linking chemistry and mass spectrometry, the authors determined that the organization of apoA-I was similar in discs and spheres, regardless of their size. Their findings support earlier work that proposed a "double belt" model structure for discoid HDLs, in which each of two ring-shaped apoA-I molecules wraps around a disc-like patch of enclosed lipids. In the present study, the authors propose a trefoil model, similar to the leaves of a clover, where each apoA-I in the structure bends to allow for additional molecules that shape the particle. The trefoil model provides a foundation for understanding how apoA-I structure modulates HDL function and metabolism, the authors say. — F.A.



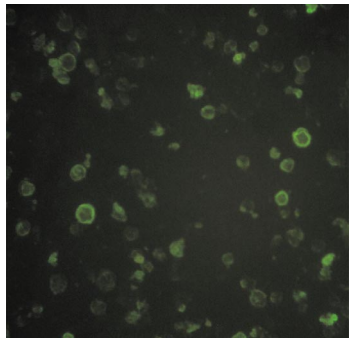
Apolipoprotein (apo)A-I on a spherical HDL particle.

"Structure of apolipoprotein A-I in spherical high-density lipoproteins of different sizes" by R. A. Gangani D. Silva, Rong Huang, Jamie Morris, Jianwen Fang, Elena O. Gracheva, Gang Ren, Anatol Kontush, W. Gray Jerome, Kerry-Anne Rye, and W. Sean Davidson (see pages 12176–12181)

MICROBIOLOGY

A redirected defense against HIV

The HIV protein gp120 binds to the CD4 receptor on helper T cells, initiating contact and infection by the virus. Most of gp120's residues are highly variable, however, making it a difficult target for antibodies. Maria Perdomo *et al.* introduce an indirect method for neutralizing HIV via gp120 that takes advantage of a large pool of antibodies already available in the body. The authors synthesized peptides corresponding to the gp120 binding site on CD4 and attached the disaccharide gal(α1,3)gal to the peptides. In humans and old world monkeys, antibodies to gal(α1,3)gal(4) are known to constitute ≈1% of the serum population. The authors hypothesized that gp120 on live HIV would bind the peptide–saccharide complex, rendering the virus vulnerable to destruction by macrophages and triggering natural killer cells to destroy infected T cells. Experiments *in vitro* with a laboratory strain of HIV supported their theory. This technique of redirecting the specificity of antibodies could provide another means for controlling HIV in the future. According to the authors, additional experiments will first have to show that the method is effective against primary HIV isolates and then demonstrate its efficacy in animals. — K.M.



Binding of anti-gal antibodies (green) from HIV-1 negative serum on the surface of ACH2 cells.

"Neutralization of HIV-1 by redirection of natural antibodies" by Maria F. Perdomo, Michael Levi, Matti Sällberg, and Anders Vahlne (see pages 12515–12520)

PLANT BIOLOGY

Expanding rice's range

The ability to grow rice—one of the world's staple food crops—in a wider range of climates and elevations could be enhanced by determining the genes that allow rice to germinate at lower temperatures. Kenji Fujino *et al.* identified one of the genes enabling low-temperature germination of rice and found similarities to high-altitude, flowering plants known as dicotyledons, or "dicots." The authors had previously identified a genetic locus, *qLTG3-1*, that accounted for ≈30% of the rice variants capable of germinating at low temperatures. In this study, they cloned the gene for this locus and found that it encoded an unknown protein. The authors observed a protective tissue covering the seed that had to be weakened before the seedling could emerge. Their evidence linking *qLTG3-1* with the seed covering suggests that monocots (such as rice) and dicots may have similar germination processes. Knowing that the gene is active in low-temperature germination could help plant breeders develop rice cultivars suited to cooler areas, the authors say. — T.H.D.

Germination of modified rice varieties incubated for 7 days at 15°C.

"Molecular identification of a major quantitative trait locus, qLTG3-1*, controlling low-temperature germinability in rice" by Kenji Fujino, Hiroshi Sekiguchi, Yasuyuki Matsuda, Kazuhiko Sugimoto, Kazuko Ono, and Masahiro Yano* (see pages 12623–12628)