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In This Issue

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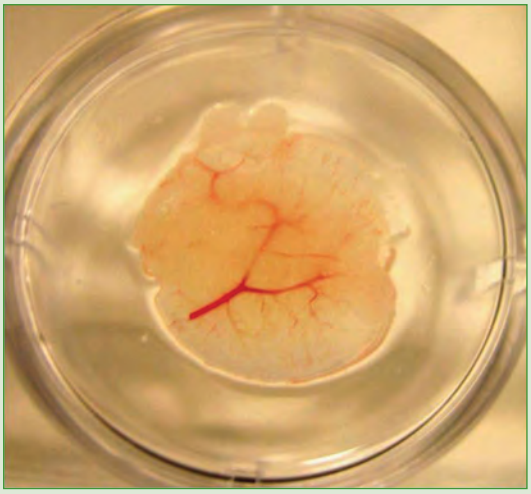
Streamlining drug development with humanized mice

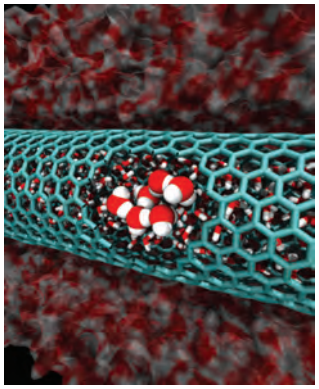


A human artificial liver implanted in the body cavity of a mouse and extracted into a culture plate.

Successful preclinical testing of experimental drugs in animal models partly relies on researchers' ability to predict whether the drugs can be safely and efficiently metabolized in humans. But differences in drug metabolism between mice and humans often render such evaluation—routinely performed during clinical trials—challenging. To address this challenge, Alice Chen et al. (pp. 11842–11847) used tissue engineering technology to develop "humanized" mice with artificial livers, built in the laboratory from human liver cells. The authors grew primary human liver cells and mouse fibroblasts together and encapsulated the cells in a chemically activated polymer scaffold. The scaffold was embedded with a peptide that boosted the cells' ability to synthesize and secrete life-sustaining molecules. The "livers" were then implanted under the skin or in the body cavity of mice. Because conditions favorable to appropriate signaling within these artificial livers had been optimized before the tissue was implanted, the authors report, the livers engrafted efficiently and the mice displayed human liver functions for weeks, including the synthesis of human proteins and human drug metabolism. The artificial livers produced functional human drug-metabolizing enzymes, helped monitor the metabolic profile of human metabolites, and helped model toxic interactions between drugs. Unlike current approaches to create chimeric mice, which typically take a long time, the authors' technique could generate humanized mice in less than 2 weeks, suggesting that humanized organs could potentially help streamline drug development by furnishing animal models that closely recapitulate human physiology, according to the authors. — P.N.

Why carbon nanotubes fill with water

Hydrophobic carbon nanotubes should repel water, which is why researchers have been perplexed by theory and experiments suggesting that water spontaneously fills the carbon nanotubes' interior. Tod Pascal et al. (pp. 11794–11798) used computer simulations to calculate thermodynamic interactions between water and carbon nanotubes (CNT) of three diameter ranges. The researchers found that for all tube sizes, the free energy of water inside CNTs decreased compared with the free energy of water in bulk, suggesting that wet CNT internal space is thermodynamically favorable. For the largest and smallest diameter tubes (less than 1 nm and greater than 1.4 nm), increases in entropy compensated for any enthalpy loss resulting from broken hydrogen bonds in the bulk liquid. In tubes with diameters between 1.1–1.2 nm, water formed a highly ordered ice-like phase, the researchers report. The authors note that the surprising interactions between CNTs and water are largely due to water's orderly tetrahedral bonding between slightly positive hydrogen atoms and slightly negative oxygen atoms. The results may help researchers design nanopores for applications such as desalination and water treatment, the authors suggest. — J.M.

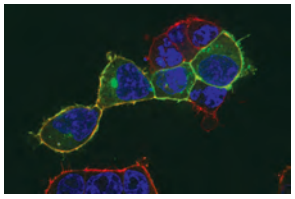


Water molecules inside a 2.0 nm CNT.

Unraveling tunicamycin's toxic effects

The antibiotic tunicamycin (TM), widely used in laboratories to encourage protein unfolding in the endoplasmic reticulum, is a potentially promising anticancer drug capable of eradicating tumor cells. So far, however, this compound, which is naturally produced by several bacteria, has proven too toxic for human use. Jan Reiling et al. (pp. 11756–11765) tackled the toxicity problem by attempting to determine what makes cells so sensitive to TM. The authors performed global gene disruption in a human cell line that, with the exception of chromosome 8, was haploid in an attempt to identify genes that, when disrupted, rendered cells resistant to toxic doses of TM. The screen identified a transporter of the major facilitator superfamily, known as major facilitator

domain containing 2A (MFSD2A), as a critical factor in determining cellular TM sensitivity. Previous studies have described various potential roles for MFSD2A, but the protein's function in transport has remained largely unexplored. The authors found that cells without MFSD2A were largely resistant to TM, while cells that overexpressed MFSD2A were hypersensitive to the antibiotic's toxic effects. The researchers propose that MFSD2A plays a critical role in TM sensitivity by allowing TM to cross the plasma membrane and enter cells. — B.A.



Localization of MFSD2A (green) in transfected cells.

Molecular axis of players might underlie type 1 diabetes

The loss of insulin-secreting beta cells from the pancreas is a feature of type 1 diabetes, an autoimmune disease that often requires lifelong treatment. Qingguo Ruan et al. (pp. 12030–12035) attempted to tease apart the molecular factors underlying the death of pancreatic beta cells by studying a gene switch known as programmed cell death protein 4 (PDCD4), which acts as a tumor suppressor. The authors previously found that mice lacking PDCD4 developed immune disorders and spontaneous tumors. To test the protein's effect on beta cells, the authors created mice deficient in PDCD4, which, compared with age-matched control mice, had significantly larger beta cell-containing pancreatic islets at 12 weeks of age. In addition, 2 days after mice were given a single high dose of the beta cell toxin streptozotocin, all of the control mice developed diabetes, whereas no more than 30% of the PDCD4-deficient mice showed signs of the disease. Further molecular analysis revealed that a microRNA—a snippet of regulatory RNA—called miR-21, implicated in cancer and immune disorders, likely lowered the levels of PDCD4 in beta cells, thus sparing the cells from programmed death. In turn, miR-21 levels were cranked up by experimentally overproducing two other gene switches in beta cells. The findings implicate a molecular axis of players that could serve as potential targets of therapeutic interventions for type 1 diabetes, according to the authors. — P.N.

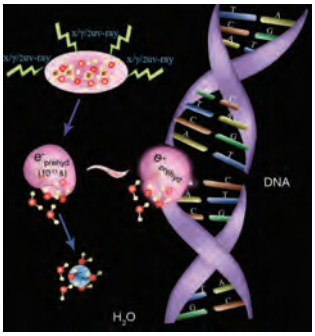
Origins of flatworms' bacterial pals

In the world of sulfur-oxidizing bacterial symbionts and their marine hosts, host types are broad and numerous but known bacterial partners fall into two classes: *Gammaproteobacteria* and *Epsilonproteobacteria*. Harald Gruber-Vodicka et al. (pp. 12078–12083) examined the bacterial symbionts of *Paracatenula* flatworms and found evidence that the bacteria represent an ancient clade of sulfur-oxidizing *Alphaproteobacteria* that coevolved with their flatworm hosts. The researchers analyzed tissue sections from three species of *Paracatenula* using transmissionelectron microscopy and determined that between a third and a half of the worms' bodies are composed of the bacteria—the highest proportion identified thus far among bacteria–metazoan endosymbionts. RNA gene analysis revealed that all 16 studied *Paracatenula* species harbored host-specific intracellular bacteria of a novel family-level clade. Genetic and phylogenic analysis suggested to the authors that the relationship between the two organisms may have originated more than 500 million years ago, during the flatworms' early evolution. The authors suggest that by comparing the early evolution of these *Alphaproteobacteria* with other mutualistic or parasitic types, researchers may be able to identify common genetic predispositions that allow members of the class to colonize eukaryotic cells. — J.M.

Paracatenula urania flatworm from the Belize Barrier Reef, with symbiotic bacteria (black).

Reductive DNA damage from ionizing radiation

Ionizing radiation is known to cause mutations and cell death through oxidative DNA damage but little is known about the effects of reductive DNA damage, or breaks in the DNA double helix caused by the reduction of weakly-bound electrons. Previous experiments have shown that a short-lived species of electron produced in liquid water under ionizing radiation, the so-called "prehydrated" electron, causes chemical bond breaks in DNA bases; and theoretical work has suggested that such bond breaks may damage DNA in a fashion similar to oxidative damage. Jenny Nguyen et al. (pp. 11778–11783) used femtosecond time-resolved laser spectroscopy to observe prehydrated electrons interacting with DNA in liquid water. Under ionizing radiation, the electrons caused single- and double-stranded breaks in aqueous DNA, and did so more efficiently than oxidizing radicals. The authors found that reductive damage is twice as effective as oxidative damage: OH radicals were responsible for only about a third of the DNA breaks caused by ionizing radiation, while the remaining two-thirds of the breaks were caused by reductive damage from prehydrated electrons. In both cases, the breaks can lead to DNA mutations, deformations, and lesions that ultimately result in cancer and underlie cancer cell death achieved through radiation therapy, according to the authors. — M.L.P.



Reductive DNA damage by prehydrated electrons.