BIOMEDICINE

Revisiting a Premature Aging Drug

Children with the rare disorder Hutchinson-Gilford progeria syndrome (HGPS) develop a constellation of health problems typically seen in the geriatric population, including severe atherosclerosis and osteoporosis, and most affected individuals die as teenagers. The disease-causing mutation lies in the *LMNA* gene, which encodes the nuclear scaffold protein lamin A, and it results in the production of an unprocessed form of lamin A that aberrantly retains a farnesyl lipid anchor and induces structural changes in the cell nucleus. The observations that farnesyltransferase inhibitors (FTIs: drugs that inhibit the enzyme that attaches the farnesyl tail to proteins) partially reversed the nuclear changes in cultured cells and ameliorated disease symptoms in mouse models of HGPS, led to the initiation of a clinical trial to test these drugs in children with the disease.

New results suggest that the concept motivating this clinical trial may require revision. To test the hypothesis that the HGPS-associated lamin A is toxic because of its farnesyl group, Yang *et al.* generated mice expressing a mutant version of lamin A that contained not only the disease-causing mutation but an additional mutation that prevented the protein from being farnesylated. Surprisingly, these mice developed the same spectrum of HGPS-like phenotypes as did mice expressing the farnesylated protein, albeit in a milder form. Thus, farnesylation of lamin A is unlikely to be a major contributor to the pathogenesis of HGPS, and the mechanism underlying the therapeutic efficacy of FTIs in the earlier preclinical studies remains unclear. — PAK

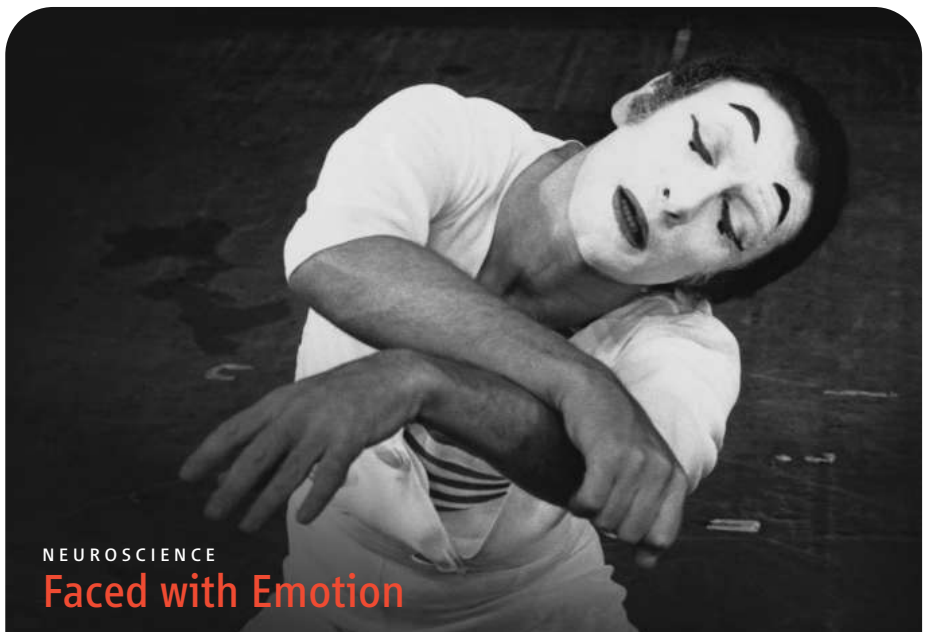
J. Clin. Invest. **118**, 10.1172/JCI35876 (2008).

IMMUNOLOGY

Responding with Restraint

Eating and breathing are essential activities, but both allow foreign substances and pathogens access to internal epithelial environments—the gut and the lungs. The immune system is poised to launch an effective attack against pathogens in the respiratory tract, yet the response must be limited to avoid collateral damage to airway tissue. Snelgrove *et al.* report that in mice, this delicate balance is maintained in part by alveolar macrophages in the lower respiratory tract; these cells express a high level of the receptor for CD200, a ligand that coats airway epithelial cells. Binding of CD200 to its receptor inhibits the secretion of inflammatory cytokines. Macrophage receptor expression normally increases during infection of lungs with influenza virus. Mice lacking CD200 showed an increase in alveolar macrophages expressing the cognate receptor, but the resolution of lung inflammation was delayed during a bout of influenza, and these animals eventually died, despite viral clearance from the lungs. Treatment with a soluble form of CD200 did not compromise viral clearance, but limited damaging inflammation. This receptor-ligand pair may be relevant to the search for drugs that dampen inflammation in respiratory conditions, such as asthma and chronic obstructive pulmonary disease, without interfering with responses that control infection. — LC

Nat. Immunol. **9**, 1074 (2008).



NEUROSCIENCE

Faced with Emotion

Humans are especially interested in faces, as a means of sending signals—witness the sizeable arc of somatosensory cortex devoted to representation of one's own face—and as a substrate for social cognition. Pitcher *et al.* describe results supporting theories of embodied cognition and emotion, which posit cognition and emotion as being shaped by our bodily movements and perceptions. They used repetitive transcranial magnetic stimulation (rTMS) to interfere with neural activity in the face areas of the somatosensory cortex while people discriminated the emotional expressions of faces (happy, sad, surprised, fearful, angry, and disgusted) and found that accuracy dropped significantly, as it also did when the occipital face area was similarly stimulated. The temporal sequence of neural processing was then delineated using double-pulse TMS, showing that the occipital area acted in the time window from 60 to 100 ms after the face stimulus was shown, whereas the somatosensory area was active a bit later, between 100 and 170 ms. — GJC

J. Neurosci. **28**, 8929 (2008).

CLIMATE SCIENCE

Waters of Life

River discharge transports nutrients such as nitrate to the sea, fueling the primary production that removes carbon dioxide from the atmosphere and thereby helps to regulate climate. Some of the atmospheric carbon dioxide fixed by this production is effectively diverted from the active carbon cycle and buried in sediments on the sea floor in a process referred to as

CREDITS (TOP TO BOTTOM): HULTON-DEUTSCH COLLECTION/CORBIS; YANG *ET AL., J. CLIN. INVEST.* **118**, 10.1172/JCI35876 (2008)

the "biological pump." It has been shown that river discharge causes significant carbon sequestration in the shelf areas near the mouths of rivers, yet it remains unclear whether its influence extends much further from the coast.

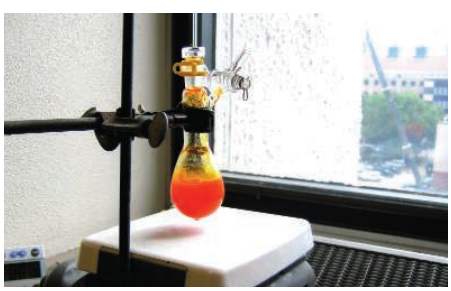
Subramaniam *et al.* report that the Amazon River plume stimulates a great deal of carbon fixation in the open ocean far off the coast, largely by stimulating diazotrophy (fixation of atmospheric nitrogen by bacteria) in surface waters. They estimate that the amount of organic carbon produced through this pathway is nearly three times as much as that resulting from the near-shore production that is supported by nitrate, and they speculate that this could be an important effect of rivers worldwide. Because river runoff is influenced by climate, this aspect of the biological pump could be affected by anthropogenic climate change as well. — HJS

Proc. Natl. Acad. Sci. U.S.A. **105**, 10460 (2008).

CHEMISTRY

A Window into Cyclization

Few carbon-based compounds absorb light in the visible portion of the spectrum. Organic photochemical reactions therefore largely rely on irradiation in the ultraviolet, which is expensive to implement on a large scale and often introduces substantial excess energy into the system, which limits selectivity. At the same time, there is a multitude of metal-bearing molecules that



absorb efficiently in the visible and have been studied thoroughly in the context of electron-transfer chemistry.

Ischay *et al.* applied one such compound, a ruthenium (Ru) complex bearing three bipyridyl ligands, toward the catalysis of enone cyclization. The substrates are two tethered C=C-C(O)-R moieties, where at least one R group must be a phenyl ring (the other can be an alkyl, alkoxy, or amide group). Upon absorbing blue light, the Ru complex can undergo an electron-transfer cycle that lends an electron to the substrate, accelerating formation of a bicyclic product via bond formation between the olefins. Placing the reaction flask by the window is sufficient for ordinary sunlight to drive the process. — JSY

J. Am. Chem. Soc. **130**, 10.1021/ja805387f (2008).

CREDIT: TEHSHIK YOON

PHYSICS

Combs with Tunable Teeth

The generation of optical combs—broadband light made up of individual frequency components, equally spaced and spanning many orders of magnitude—has revolutionized metrology and spectroscopy because it provides an exact ruler with which to compare and mea sure wavelengths and spectroscopic signals. The spacing between the teeth of these optical combs, however, tends to be fixed for the system being used for light generation.

Savchenkov *et al.* introduce a generation method that allows the frequency spacing to be tuned. Using a calcium fluoride optical whispering-gallery–mode resonator, which sustains a family of resonant modes, they show that the nonlinear interaction of the laser light pumped into the cavity of the resonator generates a comb of equally spaced frequencies. By tuning the frequency of the pump laser with a particular resonant mode of the resonator, the frequency spacing of the output light comb can be shifted in a controlled manner, thereby providing an additional degree of flexibility in the generation of bespoke light. — ISO

Phys. Rev. Lett. **101**, 93902 (2008).

GENETICS

Just One Copy

Most model plant species have undergone at least one whole-genome duplication event relative to their nearest well-studied relative. The occurrence of a duplicated genome in the history of the species, even if not retained in the extant species, can confound estimates of molecular evolution. Wang *et al.* have investigated the relative rates of molecular evolution in a conserved syntenic sequence in members of the *Solanaceae* family (eggplant, pepper, petunia, potato, and tomato) that have undergone no genome-wide duplication events since they diverged, which from this study was estimated to have been ~30 million years ago. Although some regions were duplicated within individual species, the authors were able to analyze genes and regions that have, more or less, been evolving as a single copy within the genome. They identified small-scale differences in the location of insertions and deletions, lineage-specific selection, gene content, order, and orientation, and estimated that approximately one-third of the examined regions is under selection and two-thirds of the sequences under selection are outside of genes and not associated with domestication. — LMZ

Genetics **179**, 10.1534/genetics.108.087981 (2008).

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