EDITORS'CHOICE

EDITED BY KRISTEN MUELLER AND MARIA CRUZ

PLANETARY SCIENCE

Debating the Grandest Canyon

Valles Marineris is a prominent trough on Mars that extends for several thousands of kilometers and is 5 to 10 km deep, the longest, deepest canyon in the solar system (the Grand Canyon is less than 2 km deep). Although it lies on the edge of Mars' giant volcano Tharsis, the formation of Valles Marineris has been debated. Two recent papers provide a thorough discussion of previous models and approach the canyon's formation in different ways. Andrews-Hanna, in a final of three papers analyzing the feature, proposes that the trough formed as a direct result of Tharsis—the mass of this giant volcanic center is not fully supported by the underlying crust, and it formed in part over a preexisting tectonic boundary on Mars. Volcanism focused along this boundary could have weakened the crust, allowing localized subsidence and flow of the crust at depth, forming the trough. Yin mapped the geology along Valles Marineris in detail in several areas and argues that left-lateral strike-slip faulting along the trough, yielding displacement of more than 100 km, was important. Such faulting can enhance subsidence, as seen on Earth in places such as the Dead Sea Basin and Death Valley. Neither model requires large amounts of extension across the trough. — BH

J. Geophys. Res. **117**, 10.1029/2012JE004059 (2012); *Lithosphere* **4**, 10.1130/L192.1 (2012).

POLICY

Spend for a Cure?

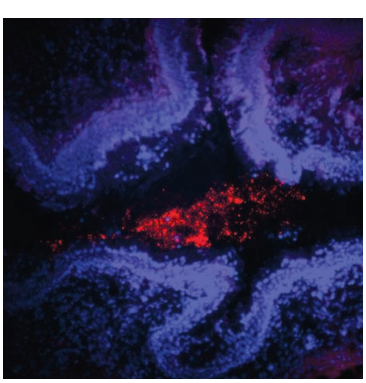
Advocates for public spending on biomedical research proclaim the importance of such investments in developing treatments for disease. Government-funded research indeed affects aspects of commercial drug development. Yet many features of this relationship remain unclear. Blume-Kohout compiled longitudinal data from six sources, including a commercial database of pharmaceutical R&D, and National Institutes of Health (NIH) project descriptions and awards. She analyzed how changes in the way NIH allocated research funds targeting 67 different diseases affected the number of drugs being developed to treat those diseases. Consistent with prior research, analysis of grants awarded from 1975 through 2006 showed that a sustained 10% funding increase targeting a specific disease led to a 4.5% increase in the number of drugs targeting that disease entering Phase I clinical trials, with a lag of up to 12 years. In contrast, she found no evidence that changes in the allocation of funds across the NIH disease portfolio affect industry's decisions to invest in Phase III clinical trials for treatments for those diseases. Thus, NIH funding influences the early stages of drug discovery and testing but may not affect the later, more costly stages of drug development. — BW

J. Pol. Anal. Manag. **31**, 641 (2012).

BIOMATERIALS

The Great Mucus Barrier

Mucus is often thought of as a nuisance when you have a bad cold or runny nose, but this is only one aspect of its broader use by the body to filter out foreign materials. Its tenacity in grabbing onto particulate matter also makes it difficult to deliver drugs to tissues that are protected by a mucus layer, such as the vaginal tissues, but delivery and sustained dosing to this region could aid in the prevention of sexually transmitted diseases or cervical cancer. Ensign *et al.* designed mucus-penetrating particles by coating either carboxylic acid–coated polystyrene nanoparticles or poly(lactic-co-glycolic acid) nanoparticles with a dense layer of polyethylene glycol.



When administered in a hypotonic solution to mice, the regular particles got trapped in the cervicovaginal mucus layer, whereas the coated particles covered the entire vaginal epithelium, including that of the vaginal folds, in less than 10 min. In tests on the delivery of small molecules using the particles as part of a vaginal gel, the coated particles showed not only greater but also much more uniform coverage, and there was retention of the small molecules a full day after administration. In a final demonstration, modified acyclovir, a drug for treating herpes simplex 2, was loaded into the particles and compared with a soluble form of the drug. Whereas almost 90% of the mice became infected with HSV2 in the latter case, the drug-loaded coated particles provided protection for more than half the mice. — MSL

Sci. Transl. Med. **4**, 138ra79 (2012).

NEUROSCIENCE

Decoding Depression Circuits

Fluoxetine is a widely prescribed antidepressant that acts as a selective serotonin reuptake inhibitor. Schmidt *et al.* define a particular set of neurons in the mouse brain that can mediate the effects of this drug. They focused on a set of neurons in the cerebral cortex that extend to the striatum and express the adapter protein p11 (encoded by the *S100a10* gene). p11 is

CREDITS (TOP TO BOTTOM): NASA/JPL-CALTECH; L. M. ENSIGN *ET AL.*, *SCI. TRANSL. MED.*, **4**, 138RA79 (2012)

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known to stabilize the expression of serotonin receptors at the cell surface, and the loss of p11 is associated with depressive behaviors. The authors used a translational profiling method to monitor a specific set of neurons in the cerebral cortex that express p11 and found that they specifically responded to fluoxetine. Depletion of p11 in the cortex showed that these neurons were required for the behavioral effects of the drug. Thus, changes in signaling through serotonin receptors in p11-expressing cells appear to account for the beneficial effect of fluoxetine. However, depletion of p11 was not sufficient to cause depression-like behavior. Thus, in this case, as might be expected for complex disorders such as depression, the cell types that mediate the therapeutic response apparently do not represent the anatomical location of the original genesis of the disease. — LBR

Cell **149**, 1152 (2012).

EVOLUTION

Ecology Splits Genomes

Evolutionary biologists wish to know how the environment and specialization of a species factor into the process of speciation. Nosil *et al*. present single-nucleotide polymorphism (SNP) data from eight populations of stick insects (*Timema cristinae*) that use two different plant species as their hosts, show slight phenotypic differences, and are in the process of speciation. Using a Bayesian model to estimate the differences between the expected and observed allele frequencies and to perform pairwise comparisons among the populations, the authors executed a genome-wide assessment of the genomic signatures related to the host-specific divergence and other ecological and evolutionary factors. As expected, the authors observed an excess of highly divergent polymorphisms between population pairs experiencing mating isolation. Isolation by distance, however, and a correlation between allele frequencies and climatic variables appear to also influence the genomic variation between populations. Thus, these analyses suggest that multiple ecological and evolutionary factors affect the speciation process, and it cannot be explained solely by the shift in plant host use. — LMZ

Proc. R. Soc. London. Ser. B **279**, 10.1098/rspb.2012.0813 (2012).

MATERIALS SCIENCE

Locating Lithium in Oxide Anodes

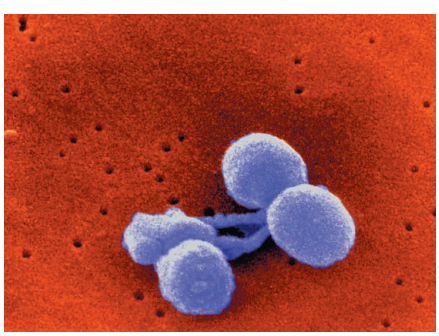
Lithium titanate anodes are finding use in applications such as electric vehicles, where high charging and discharging rates are needed. Lu *et al*. have studied a model material, the spinel $Li_4Ti_{55}O_{12}$, using a spherical-aberration–corrected scanning transmission electron microscopy technique. This method can locate lithium ions despite their inherent low contrast, given their low atomic number. The authors examined half-charged materials and could observe a sharp interface between the $Li_4Ti_{55}O_{12}$ and $Li_7Ti_{55}O_{12}$; the Ti and O columns are well aligned between these phases, but the Li ions shifted lattice sites, which is consistent with the lack of strain between these phases. They also show that the charge state of the Ti atoms is heterogeneous, and the presence of these local changes in valence is consistent with calculations that reveal strong lithium-electron interactions. — PDS

Adv. Mater. **24**, 3233 (2012).

IMMUNOLOGY

A One-Two Punch

It's well known that viral infection can leave you susceptible to bacterial infections—a bad cold or flu followed by pneumonia is a well-known and oft-experienced example. But why? Negishi *et al*. now reveal a potential mechanism. They find that triggering of RIG-I–like receptors (RLRs), which are most often triggered by viruses, can inhibit Toll-like receptor (TLR)



signaling, which is essential for some antibacterial responses. In particular, RLR signaling induces the transcription factor IRF3, which binds to and blocks the transcriptional activation of *Il12b*. *Il12b* encodes the p40 subunit of the cytokine interleukin-12—a molecule very important to the defense against bacterial infections. In mice, activation of RLRs led to attenuated TLR signaling and consequently, decreased T cell responses dependent on IL-12 and another cytokine that uses p40, IL-23. The consequence of such reduced immunity was that mice succumbed to sublethal doses of a bacterial infection if they were first infected with a virus. — KLM

Nat. Immunol. **13**, 659 (2012).

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