
**This month in *Science* Roundup:**



## Structural basis for antibody-mediated neutralization of Lassa virus

**Abstract:** The arenavirus Lassa causes severe hemorrhagic fever and a significant disease burden in West Africa every year. The glycoprotein, GPC, is the sole antigen expressed on the viral surface and the critical target for antibody-mediated neutralization. Here we present the crystal structure of the trimeric, prefusion ectodomain of Lassa GP bound to a neutralizing

antibody from a human survivor at 3.2-angstrom resolution. The antibody extensively anchors two monomers together at the base of the trimer, and biochemical analysis suggests that it neutralizes by inhibiting conformational changes required for entry. This work illuminates pH-driven conformational changes in both receptor-binding and fusion subunits of Lassa virus, illustrates the unique assembly of the arenavirus glycoprotein spike, and provides a much-needed template for vaccine design against these threats to global health. .
Supporting online material

### A genetic signature of the evolution of loss of flight in the Galapagos cormorant

**Abstract:** We have a limited understanding of the genetic and molecular basis of evolutionary changes in the size and proportion of limbs. We studied wing and pectoral skeleton reduction leading to flightlessness in the Galapagos cormorant (*Phalacrocorax harrisi*). We sequenced and de novo assembled the genomes of four cormorant species and applied a predictive and comparative genomics approach to find candidate variants that may have contributed to the evolution of flightlessness. These analyses and cross-species experiments in *Caenorhabditis elegans* and in chondrogenic cell lines implicated variants in genes necessary for transcriptional regulation and function of the primary cilium. Cilia are essential for Hedgehog signaling, and humans affected by skeletal ciliopathies suffer from premature bone growth arrest, mirroring skeletal features associated with loss of flight.
Supporting online material

### Massive blow-out craters formed by hydrate-controlled methane expulsion from the Arctic seafloor

**Abstract:** Widespread methane release from thawing Arctic gas hydrates is a major concern, yet the processes, sources, and fluxes involved remain unconstrained. We present geophysical data documenting a cluster of kilometer-wide craters and mounds from the Barents Sea floor associated with large-scale methane expulsion. Combined with ice sheet/gas hydrate modeling, our results indicate that during glaciation, natural gas migrated from underlying hydrocarbon reservoirs and was sequestered extensively as subglacial gas hydrates. Upon ice sheet retreat, methane from this hydrate reservoir concentrated in massive mounds before being abruptly released to form craters. We propose that these processes were likely widespread across past glaciated petroleum provinces and that they also provide an analog for the potential future destabilization of subglacial gas hydrate reservoirs beneath contemporary ice sheets.
Supporting online material

### Palladium-catalyzed carbon-sulfur or carbon-phosphorus bond metathesis by reversible arylation

**Abstract:** Compounds bearing aryl-sulfur and aryl-phosphorus bonds have found numerous applications in drug development, organic materials, polymer science, and homogeneous catalysis. We describe palladium-catalyzed metathesis reactions of both compound classes, each of which proceeds through a reversible arylation manifold. The synthetic power and immediate utility of this approach are demonstrated in several applications that would be

challenging to achieve by means of traditional cross-coupling methods. The C($sp^2$)–S bond metathesis protocol was used in the depolymerization of a commercial thermoplastic polymer and in the late-stage derivatization of a drug. The C($sp^2$)–P variant led to the convenient preparation of a variety of phosphorus heterocycles, including a potential chiral ligand and fluorescent organic materials, via a ring-closing transformation.
Supporting online material

## Polymeric peptide pigments with sequence-encoded properties

**Abstract:** Melanins are a family of heterogeneous polymeric pigments that provide ultraviolet (UV) light protection, structural support, coloration, and free radical scavenging. Formed by oxidative oligomerization of catecholic small molecules, the physical properties of melanins are influenced by covalent and noncovalent disorder. We report the use of tyrosine-containing tripeptides as tunable precursors for polymeric pigments. In these structures, phenols are presented in a (supra-)molecular context dictated by the positions of the amino acids in the peptide sequence. Oxidative polymerization can be tuned in a sequence-dependent manner, resulting in peptide sequence–encoded properties such as UV absorbance, morphology, coloration, and electrochemical properties over a considerable range. Short peptides have low barriers to application and can be easily scaled, suggesting near-term applications in cosmetics and biomedicine.
Supporting online material

## Activity-based protein profiling reveals off-target proteins of the FAAH inhibitor BIA 10-2474

**Abstract:** A recent phase 1 trial of the fatty acid amide hydrolase (FAAH) inhibitor BIA 10-2474 led to the death of one volunteer and produced mild-to-severe neurological symptoms in four others. Although the cause of the clinical neurotoxicity is unknown, it has been postulated, given the clinical safety profile of other tested FAAH inhibitors, that off-target activities of BIA 10-2474 may have played a role. Here we use activity-based proteomic methods to determine the protein interaction landscape of BIA 10-2474 in human cells and tissues. This analysis revealed that the drug inhibits several lipases that are not targeted by PF04457845, a highly selective and clinically tested FAAH inhibitor. BIA 10-2474, but not PF04457845, produced substantial alterations in lipid networks in human cortical neurons, suggesting that promiscuous lipase inhibitors have the potential to cause metabolic dysregulation in the nervous system.
Supporting online material

## Early life stress confers lifelong stress susceptibility in mice via ventral tegmental area OTX2

**Abstract:** Early life stress increases risk for depression. Here we establish a “two-hit” stress model in mice wherein stress at a specific postnatal period increases susceptibility to adult social defeat stress and causes long-lasting transcriptional alterations that prime the ventral tegmental area (VTA)—a brain reward region—to be in a depression-like state. We identify a role for the developmental transcription factor orthodenticle homeobox 2 *(Otx2)* as an upstream mediator of these enduring effects. Transient juvenile—but not adult—knockdown of *Otx2* in

VTA mimics early life stress by increasing stress susceptibility, whereas its overexpression reverses the effects of early life stress. This work establishes a mechanism by which early life stress encodes lifelong susceptibility to stress via long-lasting transcriptional programming in VTA mediated by *Otx2*.
Supporting online material

## Kilogram-scale prexasertib monolactate monohydrate synthesis under continuous-flow CGMP conditions

**Abstract:** Advances in drug potency and tailored therapeutics are promoting pharmaceutical manufacturing to transition from a traditional batch paradigm to more flexible continuous processing. Here we report the development of a multistep continuous-flow CGMP (current good manufacturing practices) process that produced 24 kilograms of prexasertib monolactate monohydrate suitable for use in human clinical trials. Eight continuous unit operations were conducted to produce the target at roughly 3 kilograms per day using small continuous reactors, extractors, evaporators, crystallizers, and filters in laboratory fume hoods. Success was enabled by advances in chemistry, engineering, analytical science, process modeling, and equipment design. Substantial technical and business drivers were identified, which merited the continuous process. The continuous process afforded improved performance and safety relative to batch processes and also improved containment of a highly potent compound..
Supporting online material

## Satellites reveal contrasting responses of regional climate to the widespread greening of Earth

**Abstract:** Changes in vegetation cover associated with the observed greening may affect several biophysical processes, whose net effects on climate are unclear. We analyzed remotely sensed dynamics in leaf area index (LAI) and energy fluxes in order to explore the associated variation in local climate. We show that the increasing trend in LAI contributed to the warming of boreal zones through a reduction of surface albedo and to an evaporation-driven cooling in arid regions. The interplay between LAI and surface biophysics is amplified up to five times under extreme warm-dry and cold-wet years. Altogether, these signals reveal that the recent dynamics in global vegetation have had relevant biophysical impacts on the local climates and should be considered in the design of local mitigation and adaptation plans.
Supporting online material

## Avian egg shape: Form, function, and evolution

**Abstract:** Avian egg shape is generally explained as an adaptation to life history, yet we currently lack a global synthesis of how egg-shape differences arise and evolve. Here, we apply morphometric, mechanistic, and macroevolutionary analyses to the egg shapes of 1400 bird species. We characterize egg-shape diversity in terms of two biologically relevant variables, asymmetry and ellipticity, allowing us to quantify the observed morphologies in a two-dimensional morphospace. We then propose a simple mechanical model that explains the observed egg-shape diversity based on geometric and material properties of the egg membrane. Finally, using phylogenetic models, we show that egg shape correlates with flight

ability on broad taxonomic scales, suggesting that adaptations for flight may have been critical drivers of egg-shape variation in birds.
Supporting online material

### Breaking Lorentz reciprocity to overcome the time-bandwidth limit in physics and engineering

**Abstract:** A century-old tenet in physics and engineering asserts that any type of system, having bandwidth Δω, can interact with a wave over only a constrained time period Δ*t* inversely proportional to the bandwidth (Δt·Δω ~ 2π). This law severely limits the generic capabilities of all types of resonant and wave-guiding systems in photonics, cavity quantum electrodynamics and optomechanics, acoustics, continuum mechanics, and atomic and optical physics but is thought to be completely fundamental, arising from basic Fourier reciprocity. We propose that this "fundamental" limit can be overcome in systems where Lorentz reciprocity is broken. As a system becomes more asymmetric in its transport properties, the degree to which the limit can be surpassed becomes greater. By way of example, we theoretically demonstrate how, in an astutely designed magnetized semiconductor heterostructure, the above limit can be exceeded by orders of magnitude by using realistic material parameters. Our findings revise prevailing paradigms for linear, time-invariant resonant systems, challenging the doctrine that high-quality resonances must invariably be narrowband and providing the possibility of developing devices with unprecedentedly high time-bandwidth performance.
Supporting online material

### Human-in-the-loop optimization of exoskeleton assistance during walking

**Abstract:** Exoskeletons and active prostheses promise to enhance human mobility, but few have succeeded. Optimizing device characteristics on the basis of measured human performance could lead to improved designs. We have developed a method for identifying the exoskeleton assistance that minimizes human energy cost during walking. Optimized torque patterns from an exoskeleton worn on one ankle reduced metabolic energy consumption by 24.2 ± 7.4% compared to no torque. The approach was effective with exoskeletons worn on one or both ankles, during a variety of walking conditions, during running, and when optimizing muscle activity. Finding a good generic assistance pattern, customizing it to individual needs, and helping users learn to take advantage of the device all contributed to improved economy. Optimization methods with these features can substantially improve performance.
Supporting online material

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**In *Science Signaling***

### Intercellular transmission of the unfolded protein response promotes survival and drug resistance in cancer cells

**Abstract:** Increased protein translation in cells and various factors in the tumor microenvironment can induce endoplasmic reticulum (ER) stress, which initiates the unfolded protein response (UPR). We have previously reported that factors released from cancer cells

mounting a UPR induce a de novo UPR in bone marrow–derived myeloid cells, macrophages, and dendritic cells that facilitates protumorigenic characteristics in culture and tumor growth in vivo. We investigated whether this intercellular signaling, which we have termed transmissible ER stress (TERS), also operates between cancer cells and what its functional consequences were within the tumor. We found that TERS signaling induced a UPR in recipient human prostate cancer cells that included the cell surface expression of the chaperone GRP78. TERS also activated Wnt signaling in recipient cancer cells and enhanced resistance to nutrient starvation and common chemotherapies such as the proteasome inhibitor bortezomib and the microtubule inhibitor paclitaxel. TERS-induced activation of Wnt signaling required the UPR kinase and endonuclease IRE1. However, TERS-induced enhancement of cell survival was predominantly mediated by the UPR kinase PERK and a reduction in the abundance of the transcription factor ATF4, which prevented the activation of the transcription factor CHOP and, consequently, the induction of apoptosis. When implanted in mice, TERS-primed cancer cells gave rise to faster growing tumors than did vehicle-primed cancer cells. Collectively, our data demonstrate that TERS is a mechanism of intercellular communication through which tumor cells can adapt to stressful environments.

## IRE1α promotes viral infection by conferring resistance to apoptosis

**Abstract:** The unfolded protein response (UPR) is an ancient cellular pathway that detects and alleviates protein-folding stresses. The UPR components X-box binding protein 1 (XBP1) and inositol-requiring enzyme 1α (IRE1α) promote type I interferon (IFN) responses. We found that *Xbp1*-deficient mouse embryonic fibroblasts and macrophages had impaired antiviral resistance. However, this was not because of a defect in type I IFN responses but rather an inability of *Xbp1*-deficient cells to undergo viral-induced apoptosis. The ability to undergo apoptosis limited infection in wild-type cells. *Xbp1* -deficient cells were generally resistant to the intrinsic pathway of apoptosis through an indirect mechanism involving activation of the nuclease IRE1α. We observed an IRE1α-dependent reduction in the abundance of the proapoptotic microRNA miR-125a and a corresponding increase in the amounts of the members of the antiapoptotic Bcl-2 family. The activation of IRE1α by the hepatitis C virus (HCV) protein NS4B in XBP1-proficient cells also conferred apoptosis resistance and promoted viral replication. Furthermore, we found evidence of IRE1α activation and decreased miR-125a abundance in liver biopsies from patients infected with HCV compared to those in the livers of healthy controls. Our results reveal a prosurvival role for IRE1α in virally infected cells and suggest a possible target for IFN-independent antiviral therapy.

## The lncRNA H19 mediates breast cancer cell plasticity during EMT and MET plasticity by differentially sponging miR-200b/c and let-7b

**Abstract:** Metastasis is a multistep process by which tumor cells disseminate from their primary site and form secondary tumors at a distant site. The pathophysiological course of metastasis is mediated by the dynamic plasticity of cancer cells, which enables them to shift between epithelial and mesenchymal phenotypes through a transcriptionally regulated program termed epithelial-to-mesenchymal transition (EMT) and its reverse process, mesenchymal-to-epithelial transition (MET). Using a mouse model of spontaneous metastatic breast cancer, we investigated the molecular mediators of metastatic competence within a heterogeneous

primary tumor and how these cells then manipulated their epithelial-mesenchymal plasticity during the metastatic process. We isolated cells from the primary mammary tumor, the circulation, and metastatic lesions in the lung in TA2 mice and found that the long noncoding RNA (lncRNA) H19 mediated EMT and MET by differentially acting as a sponge for the microRNAs miR-200b/c and let-7b. We found that this ability enabled H19 to modulate the expression of the microRNA targets *Git2* and *Cyth3* , respectively, which encode regulators of the RAS superfamily member adenosine 5′-diphosphate (ADP) ribosylation factor (ARF), a guanosine triphosphatase (GTPase) that promotes cell migration associated with EMT and disseminating tumor cells. Decreasing the abundance of H19 or manipulating that of members in its axis prevented metastasis from grafts in syngeneic mice. Abundance of H19, GIT2, and CYTH3 in patient samples further suggests that H19 might be exploited as a biomarker for metastatic cells within breast tumors and perhaps as a therapeutic target to prevent metastasis.

### Ligand- and voltage-gated $Ca^{2+}$ channels differentially regulate the mode of vesicular neuropeptide release in mammalian sensory neurons

**Abstract:** Neuropeptides released from dorsal root ganglion (DRG) neurons play essential roles in the neurotransmission of sensory inputs, including those underlying nociception and pathological pain. Neuropeptides are released from intracellular vesicles through two modes: a partial release mode called “kiss-and-run” (KAR) and a full release mode called “full fusion–like” (FFL). Using total internal reflection fluorescence (TIRF) microscopy, we traced the release of pH-sensitive green fluorescent protein–tagged neuropeptide Y (pHluorin-NPY) from individual dense-core vesicles in the soma and axon of single DRG neurons after $Ca^{2+}$ influx through either voltage-gated $Ca^{2+}$ channels (VGCCs) or ligand-gated transient receptor potential vanilloid 1 (TRPV1) channels. We found that $Ca^{2+}$ influx through VGCCs stimulated FFL and a greater single release of neuropeptides. In contrast, $Ca^{2+}$ influx through TRPV1 channels stimulated KAR and a pulsed but prolonged release of neuropeptides that was partially mediated by Dynamin 1, which limits fusion pore expansion. Suppressing the $Ca^{2+}$ gradient to an extent similar to that seen after TRPV1 activation abolished the VGCC preference for FFL. The findings suggest that by generating a steeper $Ca^{2+}$ gradient, VGCCs promote a more robust fusion pore opening that facilitates FFL. Thus, KAR and FFL release modes are differentially regulated by the two principal types of $Ca^{2+}$ -permeable channels in DRG neurons.

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**In *Science Translational Medicine***

### Functional neuroimaging of high-risk 6-month-old infants predicts a diagnosis of autism at 24 months of age

**Abstract:** Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by social deficits and repetitive behaviors that typically emerge by 24 months of age. To develop effective early interventions that can potentially ameliorate the defining deficits of ASD and improve long-term outcomes, early detection is essential. Using prospective neuroimaging of

59 6-month-old infants with a high familial risk for ASD, we show that functional connectivity magnetic resonance imaging correctly identified which individual children would receive a research clinical best-estimate diagnosis of ASD at 24 months of age. Functional brain connections were defined in 6-month-old infants that correlated with 24-month scores on measures of social behavior, language, motor development, and repetitive behavior, which are all features common to the diagnosis of ASD. A fully cross-validated machine learning algorithm applied at age 6 months had a positive predictive value of 100% [95% confidence interval (CI), 62.9 to 100], correctly predicting 9 of 11 infants who received a diagnosis of ASD at 24 months (sensitivity, 81.8%; 95% CI, 47.8 to 96.8). All 48 6-month-old infants who were not diagnosed with ASD were correctly classified [specificity, 100% (95% CI, 90.8 to 100); negative predictive value, 96.0% (95% CI, 85.1 to 99.3)]. These findings have clinical implications for early risk assessment and the feasibility of developing early preventative interventions for ASD.

### Combined immune checkpoint blockade as a therapeutic strategy for *BRCA1*-mutated breast cancer

**Abstract:** Immune checkpoint inhibitors have emerged as a potent new class of anticancer therapy. They have changed the treatment landscape for a range of tumors, particularly those with a high mutational load. To date, however, modest results have been observed in breast cancer, where tumors are rarely hypermutated. Because *BRCA1*-associated tumors frequently exhibit a triple-negative phenotype with extensive lymphocyte infiltration, we explored their mutational load, immune profile, and response to checkpoint inhibition in a *Brca1*-deficient tumor model. *BRCA1* -mutated triple-negative breast cancers (TNBCs) exhibited an increased somatic mutational load and greater numbers of tumor-infiltrating lymphocytes, with increased expression of immunomodulatory genes including *PDCD1 (PD-1)* and *CTLA4*, when compared to TNBCs from *BRCA1*–wild-type patients. Cisplatin treatment combined with dual anti–programmed death-1 and anti–cytotoxic T lymphocyte–associated antigen 4 therapy substantially augmented antitumor immunity in *Brca1*-deficient mice, resulting in an avid systemic and intratumoral immune response. This response involved enhanced dendritic cell activation, reduced suppressive $FOXP3^+$ regulatory T cells, and concomitant increase in the activation of tumor-infiltrating cytotoxic $CD8^+$ and $CD4^+$ T cells, characterized by the induction of polyfunctional cytokine-producing T cells. Dual (but not single) checkpoint blockade together with cisplatin profoundly attenuated the growth of *Brca1*-deficient tumors in vivo and improved survival. These findings provide a rationale for clinical studies of combined immune checkpoint blockade in *BRCA1*-associated TNBC.

### Sulforaphane reduces hepatic glucose production and improves glucose control in patients with type 2 diabetes

**Abstract:** A potentially useful approach for drug discovery is to connect gene expression profiles of disease-affected tissues (“disease signatures”) to drug signatures, but it remains to be shown whether it can be used to identify clinically relevant treatment options. We analyzed coexpression networks and genetic data to identify a disease signature for type 2 diabetes in liver tissue. By interrogating a library of 3800 drug signatures, we identified sulforaphane as a compound that may reverse the disease signature. Sulforaphane suppressed glucose

production from hepatic cells by nuclear translocation of nuclear factor erythroid 2–related factor 2 (NRF2) and decreased expression of key enzymes in gluconeogenesis. Moreover, sulforaphane reversed the disease signature in the livers from diabetic animals and attenuated exaggerated glucose production and glucose intolerance by a magnitude similar to that of metformin. Finally, sulforaphane, provided as concentrated broccoli sprout extract, reduced fasting blood glucose and glycated hemoglobin (HbA1c) in obese patients with dysregulated type 2 diabetes.

### The long noncoding RNA *Wisper* controls cardiac fibrosis and remodeling

**Abstract:** Long noncoding RNAs (lncRNAs) are emerging as powerful regulators of cardiac development and disease. However, our understanding of the importance of these molecules in cardiac fibrosis is limited. Using an integrated genomic screen, we identified *Wisper* (Wisp2 super-enhancer–associated RNA) as a cardiac fibroblast–enriched lncRNA that regulates cardiac fibrosis after injury. *Wisper* expression was correlated with cardiac fibrosis both in a murine model of myocardial infarction (MI) and in heart tissue from human patients suffering from aortic stenosis. Loss-of-function approaches in vitro using modified antisense oligonucleotides (ASOs) demonstrated that *Wisper* is a specific regulator of cardiac fibroblast proliferation, migration, and survival. Accordingly, ASO-mediated silencing of *Wisper* in vivo attenuated MI-induced fibrosis and cardiac dysfunction. Functionally, *Wisper* regulates cardiac fibroblast gene expression programs critical for cell identity, extracellular matrix deposition, proliferation, and survival. In addition, its association with TIA1-related protein allows it to control the expression of a profibrotic form of lysyl hydroxylase 2, implicated in collagen cross-linking and stabilization of the matrix. Together, our findings identify *Wisper* as a cardiac fibroblast–enriched super-enhancer–associated lncRNA that represents an attractive therapeutic target to reduce the pathological development of cardiac fibrosis in response to MI and prevent adverse remodeling in the damaged heart.

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**In *Science Advances***

### An innovative biologic system for photon-powered myocardium in the ischemic heart

**Abstract:** Coronary artery disease is one of the most common causes of death and disability, afflicting more than 15 million Americans. Although pharmacological advances and revascularization techniques have decreased mortality, many survivors will eventually succumb to heart failure secondary to the residual microvascular perfusion deficit that remains after revascularization. We present a novel system that rescues the myocardium from acute ischemia, using photosynthesis through intramyocardial delivery of the cyanobacterium *Synechococcus elongatus* . By using light rather than blood flow as a source of energy, photosynthetic therapy increases tissue oxygenation, maintains myocardial metabolism, and yields durable improvements in cardiac function during and after induction of ischemia. By circumventing blood flow entirely to provide tissue with oxygen and nutrients, this system has the potential to create a paradigm shift in the way ischemic heart disease is treated.

### The GH receptor exon 3 deletion is a marker of male-specific exceptional longevity

## associated with increased GH sensitivity and taller stature

**Abstract:** Although both growth hormone (GH) and insulin-like growth factor 1 (IGF-1) signaling were shown to regulate life span in lower organisms, the role of GH signaling in human longevity remains unclear. Because a GH receptor exon 3 deletion (*d3-GHR*) appears to modulate GH sensitivity in humans, we hypothesized that this polymorphism could play a role in human longevity. We report a linear increased prevalence of *d3-GHR* homozygosity with age in four independent cohorts of long-lived individuals: 841 participants [567 of the Longevity Genes Project (LGP) (8% increase; $P = 0.01$), 152 of the Old Order Amish (16% increase; $P = 0.02$), 61 of the Cardiovascular Health Study (14.2% increase; $P = 0.14$), and 61 of the French Long-Lived Study (23.5% increase; $P = 0.02$)]. In addition, mega analysis of males in all cohorts resulted in a significant positive trend with age (26% increase; $P = 0.007$), suggesting sexual dimorphism for GH action in longevity. Further, on average, LGP *d3/d3* homozygotes were 1 inch taller than the wild-type (WT) allele carriers ($P = 0.05$) and also showed lower serum IGF-1 levels ($P = 0.003$). Multivariate regression analysis indicated that the presence of *d3/d3* genotype adds approximately 10 years to life span. The LGP d3/*d3-GHR* transformed lymphocytes exhibited superior growth and extracellular signal–regulated kinase activation, to GH treatment relative to WT GHR lymphocytes (*P* less than 0.01), indicating a GH dose response. The *d3-GHR* variant is a common genetic polymorphism that modulates GH responsiveness throughout the life span and positively affects male longevity.

## Compressed glassy carbon: An ultrastrong and elastic interpenetrating graphene network

**Abstract:** Carbon's unique ability to have both $sp^2$ and sp3 bonding states gives rise to a range of physical attributes, including excellent mechanical and electrical properties. We show that a series of lightweight, ultrastrong, hard, elastic, and conductive carbons are recovered after compressing $sp^2$-hybridized glassy carbon at various temperatures. Compression induces the local buckling of graphene sheets through $sp^3$ nodes to form interpenetrating graphene networks with long-range disorder and short-range order on the nanometer scale. The compressed glassy carbons have extraordinary specific compressive strengths—more than two times that of commonly used ceramics—and simultaneously exhibit robust elastic recovery in response to local deformations. This type of carbon is an optimal ultralight, ultrastrong material for a wide range of multifunctional applications, and the synthesis methodology demonstrates potential to access entirely new metastable materials with exceptional properties.

## Ultralight, scalable, and high-temperature–resilient ceramic nanofiber sponges

**Abstract:** Ultralight and resilient porous nanostructures have been fabricated in various material forms, including carbon, polymers, and metals. However, the development of ultralight and high-temperature resilient structures still remains extremely challenging. Ceramics exhibit good mechanical and chemical stability at high temperatures, but their brittleness and sensitivity to flaws significantly complicate the fabrication of resilient porous ceramic nanostructures. We report the manufacturing of large-scale, lightweight, high-temperature resilient, three-dimensional sponges based on a variety of oxide ceramic (for example, $TiO_2$, $ZrO_2$, yttria-stabilized $ZrO_2$, and $BaTiO_3$ ) nanofibers through an efficient solution blow-spinning

process. The ceramic sponges consist of numerous tangled ceramic nanofibers, with densities varying from 8 to 40 mg/cm$^3$. In situ uniaxial compression in a scanning electron microscope showed that the $TiO_2$ nanofiber sponge exhibits high energy absorption (for example, dissipation of up to 29.6 mJ/cm$^3$ in energy density at 50% strain) and recovers rapidly after compression in excess of 20% strain at both room temperature and 400°C. The sponge exhibits excellent resilience with residual strains of only ~1% at 800°C after 10 cycles of 10% compression strain and maintains good recoverability after compression at ~1300°C. We show that ceramic nanofiber sponges can serve multiple functions, such as elasticity-dependent electrical resistance, photocatalytic activity, and thermal insulation.

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**In *Science Immunology***

## Resident memory CD8$^+$ T cells in the upper respiratory tract prevent pulmonary influenza virus infection

**Abstract:** Nasal epithelial tissue of the upper respiratory tract is the first site of contact by inhaled pathogens such as influenza virus. We show that this region is key to limiting viral spread to the lower respiratory tract and associated disease pathology. Immunization of the upper respiratory tract leads to the formation of local tissue-resident memory CD8$^+$ T cells (Trm cells). Unlike Trm cells in the lung, these cells develop independently of local cognate antigen recognition and transforming growth factor–β signaling and persist with minimal decay, representing a long-term protective population. Repertoire characterization revealed unexpected differences between lung and nasal tissue Trm cells, the composition of which was shaped by the developmental need for lung, but not nasal, Trm cells to recognize antigen within their local tissue. We show that influenza-specific Trm cells in the nasal epithelia can block the transmission of influenza virus from the upper respiratory tract to the lung and, in doing so, prevent the development of severe pulmonary disease. Our findings reveal the protective capacity and longevity of upper respiratory tract Trm cells and highlight the potential of targeting these cells to augment protective responses induced to respiratory viral vaccines.

## *Plasmodium* products persist in the bone marrow and promote chronic bone loss

**Abstract:** Although malaria is a life-threatening disease with severe complications, most people develop partial immunity and suffer from mild symptoms. However, incomplete recovery from infection causes chronic illness, and little is known of the potential outcomes of this chronicity. We found that malaria causes bone loss and growth retardation as a result of chronic bone inflammation induced by *Plasmodium* products. Acute malaria infection severely suppresses bone homeostasis, but sustained accumulation of *Plasmodium* products in the bone marrow niche induces MyD88-dependent inflammatory responses in osteoclast and osteoblast precursors, leading to increased RANKL expression and overstimulation of osteoclastogenesis, favoring bone resorption. Infection with a mutant parasite with impaired hemoglobin digestion that produces little hemozoin, a major *Plasmodium* by-product, did not cause bone loss. Supplementation of alfacalcidol, a vitamin D3 analog, could prevent the bone loss. These results highlight the risk of bone loss in malaria-infected patients and the potential

benefits of coupling bone therapy with antimalarial treatment.

### Citrullination of NF-κB p65 promotes its nuclear localization and TLR-induced expression of IL-1β and TNFα

**Abstract:** Many citrullinated proteins are known autoantigens in rheumatoid arthritis, a disease mediated by inflammatory cytokines, such as tumor necrosis factor–α (TNFα). Citrullinated proteins are generated by converting peptidylarginine to peptidylcitrulline, a process catalyzed by the peptidylarginine deiminases (PADs), including PAD1 to PAD4 and PAD6. Several major risk factors for rheumatoid arthritis are associated with heightened citrullination. However, the physiological role of citrullination in immune cells is poorly understood. We report that suppression of PAD activity attenuates Toll-like receptor–induced expression of interleukin-1β (IL-1β) and TNFα by neutrophils in vivo and in vitro but not their global transcription activity. Mechanistically, PAD4 directly citrullinates nuclear factor κB (NF-κB) p65 and enhances the interaction of p65 with importin α3, which brings p65 into the nucleus. The citrullination-enhanced interaction of p65 with importin α3 and its nuclear translocation and transcriptional activity can be attributed to citrullination of four arginine residues located in the Rel homology domain of p65. Furthermore, a rheumatoid arthritis–prone variant of PAD4, carrying three missense mutations, is more efficient in interacting with p65 and enhancing NF-κB activity. Together, these data not only demonstrate a critical role of citrullination in an NF-κB–dependent expression of IL-1β and TNFα but also provide a molecular mechanism by which heightened citrullination propagates inflammation in rheumatoid arthritis. Accordingly, attenuating p65-mediated production of IL-1β and TNFα by blocking the citrullination of p65 has great therapeutic potential in rheumatoid arthritis.

### Memory-phenotype $CD4^+$ T cells spontaneously generated under steady-state conditions exert innate $T_H1$-like effector function

**Abstract:** Conventional $CD4^+$ T cells are composed of naïve, pathogen-specific memory, and pathogen-independent memory-phenotype (MP) cells under steady state. Naïve and pathogen-specific memory cells play key roles in adaptive immunity, whereas the homeostatic mechanisms regulating the generation of MP cells and their biological functions are unclear. We show that MP cells are autonomously generated from peripheral naïve cells in the absence of infectious stimulation in a T cell receptor (TCR)– and CD28-dependent manner. We further demonstrate that MP cells contain a T-$bet^{hi}$ subpopulation that is continuously generated by environmental interleukin-12 (IL-12) and rapidly produces interferon-γ (IFN-γ) in response to IL-12 in the absence of pathogen recognition. These cells can provide nonspecific host resistance against *Toxoplasma gondii* infection while enhancing the adaptive $CD4^+$ T cell responses. Together, these findings reveal that MP cells are continuously generated from naïve precursors and have a previously undescribed innate immune function by which they produce an early, T helper cell type 1 ($T_H1$)–like protective response against pathogens.

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**In *Science Robotics***

### A robotic device using gecko-inspired adhesives can grasp and manipulate large

## objects in microgravity

**Abstract:** Grasping and manipulating uncooperative objects in space is an emerging challenge for robotic systems. Many traditional robotic grasping techniques used on Earth are infeasible in space. Vacuum grippers require an atmosphere, sticky attachments fail in the harsh environment of space, and handlike opposed grippers are not suited for large, smooth space debris. We present a robotic gripper that can gently grasp, manipulate, and release both flat and curved uncooperative objects as large as a meter in diameter while in microgravity. This is enabled by (i) space-qualified gecko-inspired dry adhesives that are selectively turned on and off by the application of shear forces, (ii) a load-sharing system that scales small patches of these adhesives to large areas, and (iii) a nonlinear passive wrist that is stiff during manipulation yet compliant when overloaded. We also introduce and experimentally verify a model for determining the force and moment limits of such an adhesive system. Tests in microgravity show that robotic grippers based on dry adhesion are a viable option for eliminating space debris in low Earth orbit and for enhancing missions in space.

## AEGIS autonomous targeting for ChemCam on Mars Science Laboratory: Deployment and results of initial science team use

**Abstract:** Limitations on interplanetary communications create operations latencies and slow progress in planetary surface missions, with particular challenges to narrow–field-of-view science instruments requiring precise targeting. The AEGIS (Autonomous Exploration for Gathering Increased Science) autonomous targeting system has been in routine use on NASA's Curiosity Mars rover since May 2016, selecting targets for the ChemCam remote geochemical spectrometer instrument. AEGIS operates in two modes; in autonomous target selection, it identifies geological targets in images from the rover's navigation cameras, choosing for itself targets that match the parameters specified by mission scientists the most, and immediately measures them with ChemCam, without Earth in the loop. In autonomous pointing refinement, the system corrects small pointing errors on the order of a few milliradians in observations targeted by operators on Earth, allowing very small features to be observed reliably on the first attempt. AEGIS consistently recognizes and selects the geological materials requested of it, parsing and interpreting geological scenes in tens to hundreds of seconds with very limited computing resources. Performance in autonomously selecting the most desired target material over the last 2.5 kilometers of driving into previously unexplored terrain exceeds 93% (where ~24% is expected without intelligent targeting), and all observations resulted in a successful geochemical observation. The system has substantially reduced lost time on the mission and markedly increased the pace of data collection with ChemCam. AEGIS autonomy has rapidly been adopted as an exploration tool by the mission scientists and has influenced their strategy for exploring the rover's environment.



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