PNAS Plus Significance Statements

Ferroelectric domain wall dynamics characterized with X-ray photon correlation spectroscopy

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The dynamics in many complex systems is essentially heterogeneous and involves a series of discrete events—in particular, local structural changes. The nature and scale of these changes may vary greatly, ranging from rearrangements of atomic positions during phase transitions to displacements of tectonic plates during earthquakes. In this work, we introduce X-ray photon correlation spectroscopy (XPCS) as a powerful tool for investigating heterogeneous dynamics of interfaces. We observe the motion of ferroelectric domain walls by means of XPCS and obtain the information about nanoscale changes, which is inaccessible for other techniques. Further experiments can provide important insights into the mechanisms of unusual properties of materials such as anomalously large piezoelectric response in relaxor-based ferroelectrics and magnetoelectric coupling in multiferroics. (See pp. E6680–E6689.)

Universal folding pathways of polyhedron nets

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What makes an object successful at thermal folding? Protein scientists study how sequence affects the pathways by which chained amino acids fold and the structures into which they fold. Here we investigate the inverse problem: Starting with a 3D object as a polyhedron we ask, which ones, among the many choices of 2D unfoldings, are able to fold most consistently? We find that these "nets" follow a universal balance between entropy loss and potential energy gain, allowing us to explain why some of their geometrical attributes (such as compactness) represent a good predictor for the folding propensity of a given shape. Our results can be used to guide the stochastic folding of nanoscale objects into drug-delivery devices and thermally folded robots. (See pp. E6690–E6696.)

Chromatin organization by an interplay of loop extrusion and compartmental segregation

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Human DNA is 2 m long and is folded into a 10-μm-sized cellular nucleus. Experiments have revealed two major features of genome organization: Segregation of alternating active and inactive regions into compartments, and formation of compacted local domains. These were hypothesized to be formed by different mechanisms: Compartments can be formed by microphase separation and domains by active, motor-driven, loop extrusion. Here, we integrate these mechanisms into a polymer model and show that their interplay coherently explains diverse experimental data for wild-type and mutant cells. Our results provide a framework for the interpretation of chromosome organization in cellular phenotypes and highlight that chromatin is a complex, active matter shaped by an interplay of phase segregation and loop extrusion. (See pp. E6697–E6706.)

Origins of equine dentistry

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The domestication of horses and adoption of horse riding were critical processes that culminated in the emergence of mounted warriors and nomadic empires that shaped world history. The constraints of horse biology and riding equipment meant that equine veterinary care, particularly of teeth, was a core component of the success of the human–horse relationship. We report the earliest evidence of equine dentistry, from the Mongolian Steppe, at 1150 BCE. Key shifts in equine dentistry practice through time can be linked first to the emergence of horseback riding and later to the use of metal bits that enabled better control of horses. The maintenance of horse health through dentistry underwrote the key role of horses in cultures and economies around the world. (See pp. E6707–E6715.)

Feasting and the evolution of cooperative social organizations circa 2300 B.P. in Paracas culture, southern Peru

Charles Stanish, Henry Tantaleán, and Kelly Knudson

A key process in cultural evolution is the development of cooperative organizations that confront the collective action problems inherent in human social interactions. We demonstrate that one classic ethnographic mechanism of cooperative social organization, the hosting of feasts, was used in an

early complex, nonstate society in the south coast of Peru ~2300 B.P. We likewise demonstrate that the catchment zone of the people and goods that participated in the feast was extensive. These data support a cultural evolutionary model of early state formation as one of a network strategy. That is, key areas across a large landscape were initially integrated into a cooperative group as opposed to a strategy of local consolidation and subsequent aggregative growth. (See pp. E6716–E6721.)

Synthetic far-red light-mediated CRISPR-dCas9 device for inducing functional neuronal differentiation

Jiawei Shao, Meiyan Wang, Guiling Yu, Sucheng Zhu, Yuanhuan Yu, Boon Chin Heng, Jiali Wu, and Haifeng Ye

We have developed an optogenetic far-red light (FRL)-activated CRISPR-dCas9 system (FACE) that is orthogonal, fine-tunable, reversible, and has robust endogenous gene-activation profiles upon stimulation with FRL, with deep tissue penetration capacity, low brightness, short illumination time, and negligible phototoxicity. The FACE device is biocompatible and meets the criteria for safe medical application in humans, providing a robust differentiation strategy for mass production of functional neural cells from induced pluripotent stem cells simply by utilizing a beam of FRL. This optogenetic device has expanded the optogenetic toolkit for precise mammalian genome engineering in many areas of basic and translational research that require precise spatiotemporal control of cellular behavior, which may in turn boost the clinical progress of optogenetics-based precision therapy. (See pp. E6722–E6730.)

Decoding on the ribosome depends on the structure of the mRNA phosphodiester backbone

Hannah E. Keedy, Erica N. Thomas, and Hani S. Zaher

Reading of the genetic code is an intricate process in which the ribosome plays an active role in ensuring that translation proceeds rapidly and accurately. Studies have revealed that the mRNA adopts an unusual structure between the P and A sites of the small ribosomal subunit, where it is significantly kinked. In this work we probed the role of the kink structure in decoding. Substitutions that disrupt this structure were found to increase the accuracy of decoding. Conversely, peptide-bond formation on difficult-to-decode codons was severely reduced when this kink structure was perturbed. Our data suggest that the rigid nature of the mRNA backbone is important for ensuring efficient codon–anticodon interactions under suboptimal conditions. (See pp. E6731–E6740.)

Amyloid seeding of transthyretin by ex vivo cardiac fibrils and its inhibition

Lorena Saelices, Kevin Chung, Ji H. Lee, Whitaker Cohn, Julian P. Whitelegge, Merrill D. Benson, and David S. Eisenberg

Transthyretin (TTR) cardiac amyloidosis is characterized by the deposition of TTR amyloid fibrils in the heart. No therapy is currently available for wild-type cardiac amyloidosis. Hereditary cases are treated by liver transplantation, a crude form of gene therapy which replaces amyloidogenic mutant TTR by the more stable wild-type form, with the goal of halting further deposition and disease progression. However, wild-type TTR continues to deposit in the heart of many patients after the procedure. Until now, seeding of TTR fibril formation has not been demonstrated in vitro. We show that patient-extracted cardiac fibrils can seed both wild-type and mutant TTR fibril formation in vitro. This process can be inhibited by structure-based peptide inhibitors, thereby providing an alternative approach to therapy. (See pp. E6741–E6750.)

S4–S5 linker movement during activation and inactivation in voltage-gated K^+ channels

Tanja Kalstrup and Rikard Blunck

Excitability in heart and nervous system is based on sensing and propagation of the membrane potential by voltage-gated ion channels. Despite the increasing availability of high-resolution structures of voltage-gated ion channels, key questions about their dynamics remain elusive. Here we followed the movements of the gating machinery on the cytosolic surface of the Shaker K_V channel by introducing a fluorescent noncanonical amino acid at different positions along the linker between voltage sensor and pore. We can thus map the movement of each position and reconstruct the dynamics of the gating machinery during activation and inactivation. Considering that the Shaker channel serves as a model system, the mechanisms are likely conserved among those K_V channels containing a sizeable S4–S5 linker. (See pp. E6751–E6759.)

Zyxin promotes colon cancer tumorigenesis in a mitotic phosphorylation-dependent manner and through CDK8-mediated YAP activation

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Zyxin is a member of the cell–cell adhesion complex and controls cell cytoskeleton and motility. Analysis from clinical samples revealed that Zyxin is highly expressed in colon cancer compared with normal tissue, suggesting an oncogenic role for Zyxin in cancer. Depletion of Zyxin resulted in significantly impaired colon cancer cell proliferation, migration, cellular transformation, and tumor formation in xenograft animal models. We also showed that Zyxin is phosphorylated by CDK1 during mitosis. Mitotic phosphorylation is required for Zyxin activity in promoting colon cancer growth. Zyxin regulates YAP activity through the colon cancer oncogene CDK8. We further showed that CDK8 directly phosphorylates YAP and promotes its activation. These observations identify the Zyxin–CDK8–YAP axis as a potential therapeutic target in cancer. (See pp. E6760–E6769.)

Mechanistic insights in transcription-coupled nucleotide excision repair of ribosomal DNA

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RNAP1 transcription, dedicated to ribosomal DNAs (rDNAs), is the first and rate-limiting step of ribosome biogenesis. rDNAs are grouped into several copies. This redundancy is important to guarantee that at low damage levels one rDNA gene can be temporarily silenced without affecting overall ribosome biogenesis. Nevertheless, when DNA repair is defective or overloaded, several rDNAs could be damaged, disturbing the whole RNAP1 transcription process and later on modifying the

ribosome content of cells. Therefore, it is of fundamental importance for the cell to maintain a functional RNAP1 transcription by repairing DNA lesions on rDNAs. In this work we identified, in mammals, the repair mechanism of rDNAs along with a specific behavior for RNAP1 after UV irradiation. (See pp. E6770–E6779.)

Minor zygotic gene activation is essential for mouse preimplantation development

Ken-ichiro Abe, Satoshi Funaya, Dai Tsukioka, Machika Kawamura, Yutaka Suzuki, Masataka G. Suzuki, Richard M. Schultz, and Fugaku Aoki

Results presented in this report demonstrate that minor zygotic gene activation (ZGA) must precede major ZGA to execute successfully the maternal-to-zygotic transition, and that the timely occurrence of minor ZGA is crucial for preimplantation development to continue beyond the two-cell stage. In addition, the results show that the gene-expression program proceeds in a step-by-step fashion, and at least initially, is not regulated by a "zygotic clock" (e.g., compaction) or cell cycle progression (e.g., major ZGA that occurs during the two-cell stage). (See pp. E6780–E6788.)

How functional traits influence plant growth and shade tolerance across the life cycle

Daniel S. Falster, Remko A. Duursma, and Richard G. FitzJohn

Plant species differ in many functional traits—features of specific tissues and allocation of energy among them. While traits have been used in many correlative approaches to describe communities and demography, it has remained unclear how and why traits should influence whole-plant growth. Here, we present a theoretical framework for understanding the effect of traits on plant growth and shade tolerance. This framework captures diverse patterns of growth in relation to size and explains why the effect of traits on growth changes through ontogeny. By disentangling the effects of plant size, light environment, and traits on growth rates, this study provides a theoretical foundation for understanding growth across diverse tree species around the world. (See pp. E6789–E6798.)

Sinking particles promote vertical connectivity in the ocean microbiome

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Prokaryotes dominate the living biomass and the biological diversity of the ocean, one of the largest ecosystems on earth. The sinking of particles is a widespread mechanism that transports materials to the deep ocean, with a significant role in the global carbon cycle. Whether this process constitutes a global dispersal pathway for prokaryotic diversity connecting surface communities to those in the dark ocean has never been tested. Here we show that surface and deep-sea prokaryotic communities are strongly connected, constituting a vast oceanic metacommunity where local assemblages are linked through the transport of sinking particles. This vertical dispersal, mediated mainly by the largest sinking particles, emerges as a fundamental process shaping the assembly and biogeography of deep ocean prokaryotic communities. (See pp. E6799–E6807.)

Conservation of mRNA quality control factor Ski7 and its diversification through changes in alternative splicing and gene duplication

Alexandra N. Marshall, Jaeil Han, Minseon Kim, and Ambro van Hoof

The rapid degradation of mRNAs that lack a stop codon is critical to fidelity of gene expression and in yeast, it requires Ski7. Ski7 function is not fully understood and *SKI7*-like genes are not apparent in other organisms. We show that in most eukaryotes Ski7 is expressed as an alternative splice isoform from the *HBS1* gene. This most conserved example of alternative splicing probably arose in the common ancestor of animals, fungi, and plants. However, in six taxa alternative splicing was replaced by duplicated genes. After each duplication the *SKI7*-like gene has undergone several changes that we analyzed experimentally. The results clarify how duplicated genes diversify, identify novel *SKI7*-like genes, and reveal changes in nonstop mRNA decay. (See pp. E6808–E6816.)

Lifelong CMV infection improves immune defense in old mice by broadening the mobilized TCR repertoire against third-party infection

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Epidemiological studies have shown a correlation between CMV infection and immune system aging, especially in elderly populations. It remains unclear whether CMV infection is a key driver of, or simply a factor associated with, aging of the immune system. We show that aging in the presence of lifelong CMV infection improves T cell immunity in old animals by broadening the immune response to a different pathogen. Animals that have aged with CMV are able to recruit novel T cells into these immune responses that are present in, but not utilized in, animals aging without CMV. These data squarely challenge the premise that CMV is solely detrimental to the aging of the adaptive immune system. (See pp. E6817–E6825.)

Identification of a new subset of lymph node stromal cells involved in regulating plasma cell homeostasis

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Lymph nodes (LNs) are sites where adaptive immunity is initiated, leading to the generation of plasma cells (PCs) secreting large amounts of antibodies that typically interfere with pathogen spread. PCs are known to depend on extrinsic factors provided by niche cells to stay alive; however, the critical niche cells are still poorly understood. Here we present evidence for a fibroblast subset within murine and human LNs that is unique to the medulla where PCs reside. These fibroblasts produce factors that positively regulate PC homeostasis, similar to macrophages. Knowing the critical niche cells may help to design intervention strategies to target this niche in the setting of autoimmune disease caused by PCs secreting autoreactive antibodies. (See pp. E6826–E6835.)

Induction of oligoclonal CD8 T cell responses against pulmonary metastatic cancer by a phospholipid-conjugated TLR7 agonist

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A major goal of cancer immunotherapy is the expansion and/or reactivation of cytotoxic $CD8^+$ T cell responses against malignant cells. We previously showed that the direct injection of toll-like receptor 7 (TLR7) agonists into primary tumors can induce tumor-specific oligoclonal T cell responses whose magnitude correlates with therapeutic efficacy. However, tumors are not always accessible to local therapy. Here, we demonstrate in murine lung metastasis models that single systemic administration of a phospholipid conjugated TLR7 agonist can also expand tumor-specific cytotoxic T cells that are shared by different animals. The expansion can be achieved without causing apparent toxicity. Similar technology combining immune repertoire analysis and immunomodulatory drugs can help to guide the development of optimal immunotherapeutic regimens in cancer patients. (See pp. E6836–E6844.)

Rsd balances (p)ppGpp level by stimulating the hydrolase activity of SpoT during carbon source downshift in *Escherichia coli*

Jae-Woo Lee, Young-Ha Park, and Yeong-Jae Seok

Most bacteria accumulate the molecular alarmone (p)ppGpp to divert resources away from growth and division toward biosynthesis under various nutrient limitations. Despite its crucial role, uncontrolled accumulation of this alarmone causes severe growth inhibition and cell death. Thus, fine-tuning the cellular (p)ppGpp level is required to ensure survival and adaptation under harsh nutritional conditions. Here, we identify Rsd as a stimulator of the (p)ppGpp-degrading activity of SpoT during carbon source downshift in *Escherichia coli*, and this regulation is controlled by the phosphorylation state of HPr, a general component of the PEP-dependent sugar transport system. This study establishes a direct link between sugar signaling and the bacterial stringent response. (See pp. E6845–E6854.)

Disruption of divisome assembly rescued by FtsN–FtsA interaction in *Escherichia coli*

Sebastien Pichoff, Shishen Du, and Joe Lutkenhaus

Cell division in *Escherichia coli* requires 12 essential proteins that assemble into the divisome in a sequential manner. Assembly starts with formation of the Z-ring and culminates with the arrival of FtsN, which triggers septal peptidoglycan synthesis. Normally, deletion of any of these 12 proteins disrupts divisome assembly and results in a division block. However, about half of these proteins can be bypassed under some conditions, raising a question of how the divisome assembles under such conditions. Here we show that these bypasses require the interaction of FtsA with FtsN and that this normally weak interaction is enhanced under these conditions, leading to the back-recruitment of the other divisome proteins to the Z-ring. (See pp. E6855–E6862.)

Antimalarial proteasome inhibitor reveals collateral sensitivity from intersubunit interactions and fitness cost of resistance

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Protozoal proteasome is a validated target for antimalarial drug development, but species selectivity of reported inhibitors is suboptimal. Here we identify inhibitors with improved selectivity for malaria proteasome β5 subunit over each active subunit of human proteasomes. These compounds kill the parasite in each stage of its life cycle. They interact synergistically with a β2 inhibitor and with artemisinin. Resistance to the β5 inhibitor arose through a point mutation in the nonproteolytic β6 subunit. The same mutation made the mutant strain more sensitive to a β2 inhibitor and less fit to withstand irradiation. These findings reveal complex interplay among proteasome subunits and introduce the prospect that combined inhibition of β2 and β5 subunits can afford synergy and thwart resistance. (See pp. E6863–E6870.)

Redundancy in synaptic connections enables neurons to learn optimally

Naoki Hiratani and Tomoki Fukai

Humans and animals are capable of rapid learning from a small dataset, which is still difficult for artificial neural networks. Recent studies further suggest that our learning speed is nearly optimal given a stream of information, but its underlying mechanism remains elusive. Here, we hypothesized that the elaborate connection structure between presynaptic axons and postsynaptic dendrites is the key element for this near-optimal learning and derived a data-efficient rule for dendritic synaptic plasticity and rewiring from Bayesian theory. We implemented this rule in a detailed neuron model of visual perceptual learning and found that the model well reproduces various known properties of dendritic plasticity and synaptic organization in cortical neurons. (See pp. E6871–E6879.)

External light activates hair follicle stem cells through eyes via an ipRGC–SCN–sympathetic neural pathway

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Intrinsically photosensitive retinal ganglion cells (ipRGCs) exhibit several important functions including the circadian photo entrainment, pupillary light reflex, alertness, and phototaxis. Whether ipRGCs regulate other physiological activities is unknown. We show that external light stimulation can activate hair follicle stem cells through the eyes via an ipRGC–suprachiasmatic nucleus–sympathetic nervous circuit. Immediately after ipRGCs are stimulated by light, the systemic sympathetic activities are

activated. In skin, the local release of norepinephrine activates hair follicle stem cells. This neural circuit enables prompt communication between peripheral tissues and the external environment. Due to the systemic activation of sympathetic activities, this circuit can also allow for timely responses to external light in other organs. It also highlights a function of ipRGCs in regulating autonomic nervous activity. (See pp. E6880–E6889.)

Genetic dissection of neuropeptide cell biology at high and low activity in a defined sensory neuron

Patrick Laurent, QueeLim Ch'ng, Maëlle Jospin, Changchun Chen, Ramiro Lorenzo, and Mario de Bono

Neuropeptides are ubiquitous modulators of behavior and physiology. They are packaged in specialized secretory organelles called dense core vesicles (DCVs) that are released upon neural stimulation. Whereas local recycling of synaptic vesicles has been investigated intensively, there are few studies on recycling of DCV proteins. We set up a paradigm to study DCVs in a neuron whose activity we can control. We validate our model by confirming many previous observations on DCV cell biology. We identify a set of genes involved in recycling of DCV proteins. We also find evidence that different mechanisms of DCV priming and exocytosis may operate at high and low neural activity. (See pp. E6890–E6899.)

Molecular profiling of reticular gigantocellularis neurons indicates that eNOS modulates environmentally dependent levels of arousal

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Certain large neurons deep in the brainstem, in the nucleus gigantocellularis (NGC), are crucial for waking up the brain from deep sleep, anesthesia, or injury. NGC neurons, which project axons to central thalamus, should be especially important because central thalamic stimulation heightens CNS arousal in animals and in human patients. We have used the retroTRAP technique to discover mRNAs enriched in such NGC neurons. One mRNA, for endothelial nitric oxide synthase (eNOS), is uniquely expressed. By experiments both on the environmental/sensory side and with respect to motoric regulation, endothelial nitric oxide expression is shown to be functionally important. Five independent lines of evidence indicate that these eNOS neurons have a significant relation with their blood supply. (See pp. E6900–E6909.)

Subsystem organization of axonal connections within and between the right and left cerebral cortex and cerebral nuclei (endbrain)

Larry W. Swanson, Joel D. Hahn, Lucas G. S. Jeub, Santo Fortunato, and Olaf Sporns

The right and left cerebral hemispheres (together forming the endbrain) support cognition and affect, and, structurally, each hemisphere consists of a cortical sheet and set of deep nuclei (often called the basal ganglia). Experimental evidence in the literature identified more than 10,000 axonal macroconnections between the 244 gray matter regions of the endbrain, and the global organizing principles of the network formed by these connections were subjected to multiresolution consensus clustering analysis. The result was a hierarchy of subsystems that has only four components at the top level and 60 components at the bottom level. Furthermore, a region's status as a connectivity hub in a network is not absolute; it depends on the size and coverage of its anatomical neighborhood. (See pp. E6910–E6919.)

Repurposing isoxazoline veterinary drugs for control of vector-borne human diseases

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Reduction in clinical cases of vector-borne diseases is strongly dependent on the ability to reduce the number of infectious insect bites. Here we describe a treatment concept based on single-dose administration of an insecticidal isoxazoline drug to a human population, which leads to killing of blood-fed insect vectors and a predicted sharp decline in disease transmission. Based on the long half-life observed in preclinical species, a single human dose of <500 mg is predicted to provide plasma exposure above the insecticidal threshold for longer than 2 months. Importantly, we show that isoxazolines are active against a range of vector species, which holds promise for expanding the concept of drug-based vector control from malaria to leishmaniasis and arboviral diseases. (See pp. E6920–E6926.)

Serum exosomes mediate delivery of arginase 1 as a novel mechanism for endothelial dysfunction in diabetes

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Endothelial dysfunction plays a crucial role in the development of diabetic vasculopathy, but the mechanisms are not fully understood. In this study, we have revealed a previously undefined importance of serum exosomes in regulating endothelial function and vascular homeostasis in diabetes. Through comparative proteomics analysis, arginase1 was found enriched in diabetic serum exosomes and can be transferred to endothelial cells to inhibit NO production, thus impairing endothelial function. This is a cell-to-cell communication mechanism first identified to contribute to vascular dysfunction in diabetes. (See pp. E6927–E6936.)

Ablation of PM20D1 reveals *N*-acyl amino acid control of metabolism and nociception

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Bioactive lipids control a wide variety of physiologic processes. We have recently identified a branch of bioactive lipid signaling mediated by *N*-acyl amino acids (NAAs) and the circulating enzyme peptidase M20 domain-containing 1 (PM20D1). Here we generate and characterize mice globally deficient in PM20D1. These PM20D1-KO mice have bidirectional changes in NAA levels in blood and tissues and exhibit a variety of metabolic and nociceptive phenotypes. Our findings elucidate the endogenous physiologic functions for NAA signaling in vivo and suggest PM20D1 inhibitors might be useful for the treatment of pain. (See pp. E6937–E6945.)

Selective fertilization with phosphite allows unhindered growth of cotton plants expressing the *ptxD* gene while suppressing weeds

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An increasing number of herbicide-resistant weeds are being reported in the United States, Argentina, and Brazil. This is becoming a global challenge for the production of several major crops, such as cotton, maize, and soybean. New strategies for weed control are required to sustain agricultural production while reducing our dependence on herbicides. Here, we report that selective fertilization of transgenic cotton, expressing a bacterial phosphite dehydrogenase (PTXD), with phosphite provides an effective way to suppress weed growth. Importantly, we show that the *ptxD*-transgenic cotton plants successfully outcompete a highly aggressive glyphosate-resistant weed. The *ptxD*/phosphite system represents one of the most promising technologies of recent times with potential to solve many of the agricultural and environmental problems that we encounter currently. (See pp. E6946–E6955.)

Human impact on the diversity and virulence of the ubiquitous zoonotic parasite *Toxoplasma gondii*

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A majority of emerging infectious diseases in humans are transmitted from animals. It is generally agreed that our behavior can influence our exposure to such pathogens, but little is known regarding our role in shaping evolution in such pathogens. Such understanding would aid in their control, to the benefit of public health. Our results indicate that expansion of agriculture influenced not only the biogeography but also the virulence of *Toxoplasma gondii*. By linking landscape ecology to parasite virulence, our framework contributes a fundamentally unique perspective on the ecology and evolution of infectious disease. (See pp. E6956–E6963.)