PNAS Plus Significance Statements

Fitness landscape of the human immunodeficiency virus envelope protein that is targeted by antibodies

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An effective vaccine for HIV is still not available, although recent hope has emerged through the discovery of antibodies capable of neutralizing diverse HIV strains. Nonetheless, there exist mutational pathways through which HIV can evade known broadly neutralizing antibody responses. An ideal vaccine would elicit broadly neutralizing antibodies that target parts of the virus's spike proteins where mutations severely compromise the virus's fitness. Here, we employ a computational approach that allows estimation of the fitness landscape (fitness as a function of sequence) of the polyprotein that comprises HIV's spike. We validate the inferred landscape through comparisons with diverse experimental measurements. The availability of this fitness landscape will aid the rational design of immunogens for effective vaccines. (See pp. E564–E573.)

Freshwater salinization syndrome on a continental scale

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Salinization and alkalinization impact water quality, but these processes have been studied separately, except in arid regions. Globally, salinization has been largely attributed to agriculture, resource extraction, and land clearing. Alkalinization has been attributed to recovery from acidification, with less recognition as an environmental issue. We show that salinization and alkalinization are linked, and trends in these processes impact most of the drainage area of the United States. Increases in salinity and alkalinity are caused by inputs of salts containing strong bases and carbonates that originate from anthropogenic sources and accelerated weathering. We develop a conceptual model unifying our understanding of salinization and alkalinization and its drivers and impacts on fresh water in North America over the past century. (See pp. E574–E583.)

Impact and cost-effectiveness of snail control to achieve disease control targets for schistosomiasis

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Schistosomiasis is an infectious disease that affects over 240 million people living in low- and middle-income countries, and is caused by parasitic worms that require snail hosts to complete its lifecycle. To improve public health control of this disease, there is growing interest in using chemical-based snail control that kills snail populations in environmental water sources, which will reduce infection rate in people. We modeled transmission of schistosomiasis and cost-effectiveness of various strategies with data from low- and high-prevalence rural Kenyan communities. Adding snail control alongside conventional mass treatment programs (instead of mass treatment programs alone) was found to be cost-effective, especially in settings with high disease burden and nonparticipation in mass treatment programs. (See pp. E584–E591.)

Preferences for moral vs. immoral traits in others are conditional

David E. Melnikoff and April H. Bailey

It is commonly argued that humans have a dominant preference for morality traits vs. immorality traits in others—that is, irrespective of the surrounding context, morality fosters liking, and immorality fosters disliking. The results of four experiments oppose this view by showing that situational goals can eliminate and even reverse the preference for morality vs. immorality in others. These findings suggest that our preference for morality vs. immorality is conditional on the demands of our current goals and cannot be attributed solely to innate, "hardwired" links or personal learning experiences. They also suggest that immoral people sometimes win public adoration, and the power that comes with it, not in spite of but precisely because of their immorality. (See pp. E592–E600.)

Structural basis of STAT2 recognition by IRF9 reveals molecular insights into ISGF3 function

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Cytokines interact with their receptors and activate JAK–STAT signaling pathways that lead to changes in gene expression. In mammals, there are seven STATs that have arisen due to gene duplication and genetic drift. STATs have similar DNA binding specificity, and how individual STATs have subfunctionalized to regulate very specific cytokine responses in cells is poorly understood. Here we describe X-ray structures that show how one STAT family member, STAT2, specifically pairs with a member of the IRF family of transcription

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factors, IRF9. Despite overall structural similarity among STAT and IRF family members, surface features in the interacting domains of IRF9 and STAT2 have diverged to enable specific interaction between these family members and to enable the antiviral response. (See pp. E601–E609.)

Troy+ brain stem cells cycle through quiescence and regulate their number by sensing niche occupancy

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Adult mammalian tissues contain stem cells that contribute to tissue homeostasis and regeneration, with potential therapeutic applications. Specialized niches regulate their fate. Here we evaluated quantitatively how the subependymal zone niche regulates neural stem cell (NSC) number in the adult mouse brain. Using knock-in reporter alleles and single-cell RNA sequencing, we show that the Wnt target *Tnfrsf19*/Troy identifies both active and quiescent NSCs. Using the Ki67-iresCreER mouse model, we found that dividing stem cells have long-term self-renewal potential. We propose a model where the fate of NSCs is coupled to their density within a closed niche. Our results suggest a new mechanism for regulating adult stem cell number, which might be deregulated in brain malignancies and in aging. (See pp. E610–E619.)

Dysregulation of cotranscriptional alternative splicing underlies CHARGE syndrome

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A timely diagnosis is key for both survival and quality of life of children with CHARGE syndrome (coloboma, heart defects, atresia of choanae, retardation of growth/development, genital abnormalities, and ear anomalies). Such diagnosis is often difficult to establish, in part because many patients test negative for mutation of *CHD7*, the only gene associated with this condition to date. Identifying additional CHARGE-associated genes would not only help resolve diagnosis issues but could also help in identifying common pathogenic mechanisms, which in turn could lead to desirable curative interventions for all patients. Here, *FAM172A* is reported as a new candidate gene for CHARGE syndrome. This discovery has allowed us to reveal a molecular process that is dysregulated in both *CHD7* mutation-positive and -negative cases, such defect being correctable in vitro with rapamycin. (See pp. E620–E629.)

ALKALs are in vivo ligands for ALK family receptor tyrosine kinases in the neural crest and derived cells

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Neuroblastoma is a pediatric tumor arising from the neural crest. Dysregulation of the receptor tyrosine kinase ALK has been linked to neuroblastoma, making it important to understand its function in native conditions. In zebrafish, a related receptor—Ltk—is also expressed in neural crest and regulates development of specific pigment cells—iridophores. Ligands activating human ALK were recently identified as the ALKAL proteins (FAM150, AUG) by biochemical means. Our data show that this ligand–receptor pair functions in vivo in the neural crest of zebrafish to drive development of iridophores. Removal of Ltk or all three zebrafish ALKALs results in larvae completely lacking these cells. Using *Drosophila* and human cell lines, we show evolutionary conservation of this important interaction. (See pp. E630–E638.)

Predicting tipping points in mutualistic networks through dimension reduction

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Complex systems in many fields, because of their intrinsic nonlinear dynamics, can exhibit a tipping point (point of no return) at which a total collapse of the system occurs. In ecosystems, environmental deterioration can lead to evolution toward a tipping point. To predict tipping point is an outstanding and extremely challenging problem. Using complex bipartite mutualistic networks, we articulate a dimension reduction strategy and establish its general applicability to predicting tipping points using a large number of empirical networks. Not only can our reduced model serve as a paradigm for understanding the tipping point dynamics in real world ecosystems for safeguarding pollinators, the principle can also be extended to other disciplines to address critical issues, such as resilience and sustainability. (See pp. E639–E647.)

Chronic anthropogenic noise disrupts glucocorticoid signaling and has multiple effects on fitness in an avian community

Nathan J. Kleist, Robert P. Guralnick, Alexander Cruz, Christopher A. Lowry, and Clinton D. Francis

Studies examining relationships among habitat disturbance, physiology, and fitness in wild animals often produce contradictory or inconclusive results, casting doubt on current conservation physiology predictive frameworks linking stress and fitness. We apply a new framework drawn from experimental systems utilizing chronic inescapable stressors to explore how noise, an environmental stimulus common to wildlife habitats worldwide, disrupts stress hormone signaling and impacts fitness. We utilize a natural experiment to show that chronic, anthropogenic noise reduced baseline corticosterone levels, increased acute corticosterone response, and, at highest amplitudes, negatively impacted multiple measures of fitness across three species of birds. Our work brings conservation physiology theory involving wild animals into needed alignment with recent theories based on chronic stress in laboratory studies. (See pp. E648–E657.)

Dual evolutionary origin of insect wings supported by an investigation of the abdominal wing serial homologs in *Tribolium*

David M. Linz and Yoshinori Tomoyasu

Acquisition of morphologically novel structures can facilitate successful radiation during evolution. The emergence of wings in hexapods represents a profound moment in eukaryotic evolution, making insects one of the most successful groups. However, the tissue that gave rise to this novel and evolutionarily crucial structure, and the mechanism that facilitated its evolution, are still under intense debate. By studying various wing-related tissues in beetles, we demonstrated that two distinct lineages of wing-related tissues are present even outside the appendage-bearing segments. This outcome supports a dual evolutionary origin of insect wings, and shows that novelty can emerge through two

previously unassociated tissues collaborating to form a new structure. (See pp. E658–E667.)

A mixed modality approach towards Xi reactivation for Rett syndrome and other X-linked disorders

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The X-chromosome harbors hundreds of disease genes, a subset of which gives rise to neurodevelopmental disorders such as Rett syndrome (RTT), fragile X syndrome, and CDKL5 syndrome. There is presently no disease-specific treatment. Here, we work toward a therapeutic program based on reactivation of the silent X chromosome to restore expression of the missing protein. We develop a mixed modality approach that combines a small-molecule inhibitor of DNA methylation and an antisense oligonucleotide against Xist RNA. This combination achieves up to 30,000-fold methyl-CpG binding protein 2 upregulation in cultured cells. In vivo modeling using a conditional *Xist* knockout and 5-aza-2′-deoxycytidine recapitulates inactive X reactivation. These findings provide proof of concept for the mixed modality approach to treat X-linked disorders, including RTT. (See pp. E668–E675.)

Genetics of the human face: Identification of large-effect single gene variants

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The human face is extraordinarily variable, and the extreme similarity of the faces of identical twins indicates that most of this variability is genetically determined. We have devised an approach to increase the chance of identifying specific large genetic effects on particular facial features, by choosing features with high heritability and selecting individuals with relatively extreme facial phenotypes for comparison with a control population. This has yielded three specific and replicated genetic variants, two for features of facial profiles, and one for the region around the eyes. Further application of these methods should enable the understanding, eventually at the molecular level, of the nature of this extraordinary genetic variability, which is such an important feature of our everyday human interactions. (See pp. E676–E685.)

Signaling by the Epstein–Barr virus LMP1 protein induces potent cytotoxic $CD4^+$ and $CD8^+$ T cell responses

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Epstein–Barr virus (EBV) drives human B cell proliferation and transformation, but also potent T cell surveillance. When surveillance fails, EBV-driven malignancies arise. T cells can be stimulated/expanded on EBV-transformed B cells for adoptive therapy. Clinical data point to the therapeutic importance of CD4 T cells, perhaps through direct cytotoxicity; the mechanism underlying such an activity remains unknown. Previous studies show that signaling by the EBV oncoprotein LMP1 enhances antigen presentation. Here, we show that $LMP1^+$ B cells provide costimulation through CD70 and OX40L to drive cytotoxic CD4 (and CD8) differentiation. In a mouse model of LMP1 (EBV)-driven lymphoma, cytotoxic CD4 cells have superior antitumor activity. These findings provide a mechanism for the EBV-mediated cytotoxic CD4 response and suggest strategies for immunotherapy in EBV-related and other cancers. (See pp. E686–E695.)

CFH and *ARMS2* genetic risk determines progression to neovascular age-related macular degeneration after antioxidant and zinc supplementation

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Age-related macular degeneration (AMD) is the leading cause of severe vision loss in the elderly and has major economic and quality-of-life impact. Prophylactic high-dose zinc and antioxidant supplements treatments are typically recommended with the assumption of homogeneously distributed benefit and risk of developing neovascular AMD. We show that individual variation at *complement factor H* and *age-related maculopathy susceptibility 2*, genes which predispose to AMD, also determines the effectiveness of nutritional prophylaxis. Some individuals paradoxically experience worsening disease with treatment, while others experience greater than average benefit. These divergent responses are difficult to identify when treatment effects have long latency. Understanding individual variations in prophylactic treatment response should inform future research and optimize health outcomes. (See pp. E696–E704.)

Impaired lymphoid extracellular matrix impedes antibacterial immunity in epidermolysis bullosa

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We describe a unique role for the lymphoid extracellular matrix in maintaining systemic innate immunity. Our findings are based on studies of the genetic skin disorder recessive dystrophic epidermolysis bullosa in which affected individuals display dramatically increased bacterial colonization of skin and mucosa. We show that the increased colonization is a consequence of loss of the protein at fault—collagen VII—from the lymphoid extracellular matrix. Our study describes an intrinsic innate immune defect resulting from a genetic connective tissue disease. Hence, the data will have broad implications for deciphering the hitherto-underestimated regulatory role of the extracellular matrix in lymphoid organs and for the understanding of pathomechanisms in disorders of the extracellular matrix. (See pp. E705–E714.)

Ibuprofen alters human testicular physiology to produce a state of compensated hypogonadism

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Concern has been raised over declining male reproductive health in humans. Our study addresses this issue by extending data showing antiandrogen effects of analgesics and suggests that such compounds may be involved in adult male reproductive problems. Using a unique combination of a randomized, controlled clinical trial and ex vivo and in vitro approaches, we report a univocal depression of important aspects of testicular function, including testosterone production, after use of over-the-counter ibuprofen. The study shows that ibuprofen use results in selective transcriptional repression of endocrine cells in the human testis. This repression results in the elevation of the stimulatory pituitary hormones, resulting in a state of compensated hypogonadism, a disorder associated with adverse reproductive and physical health disorders. (See pp. E715–E724.)

Phenotypic selection as the biological mode of epigenetic conversion and reversion in cell transformation

Harry Rubin and Andrew L. Rubin

Single exposure of a certain mouse cell line to carcinogens causes delayed neoplastic transformation of most, if not all its cells. In the absence of carcinogens, the extended maintenance at high density of another cell line or of cells recently explanted from mice leads to increased saturation density, neoplastically transformed foci in culture, and tumor formation in mice. These properties are reversed to normal by frequent passages at low cell density in high serum concentrations. Such population-wide dynamics are incompatible with somatic mutation but are characteristic of epigenetic behavior. They represent phenotypic selection of cells from a normal population which progresses either to cancer or to the reversion of transformed cells to pretreatment phenotype, depending on differing microenvironments. (See pp. E725–E732.)

Tolerogenic nanoparticles restore the antitumor activity of recombinant immunotoxins by mitigating immunogenicity

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Protein-based drugs are very active in treating cancer, but their efficacy is limited by the formation of neutralizing antidrug antibodies (ADAs). Recombinant immunotoxins are proteins that are very effective in patients with leukemia, in whom immunity is suppressed, but induce ADAs, which compromise their activity, in patients with intact immunity. Here we used an immunomodulator that is encapsulated in a nanoparticle delivery system (SVP-R) to induce specific immune tolerance to immunotoxins in mice. SVP-R induces immune tolerance, prevents ADA formation, and prevents the drug neutralization and clearance that results in restoration of its antitumor activity. Importantly, the combination is also efficacious in mice with preexisting antibodies, indicating that this approach can benefit patients who often have such antibodies. (See pp. E733–E742.)

Fenofibrate prevents skeletal muscle loss in mice with lung cancer

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The cancer anorexia cachexia syndrome (CACS) is a condition characterized by skeletal muscle degradation with no effective treatment. CACS is particularly prevalent in patients with nonsmall cell lung cancer, where it reduces quality of life and increases mortality. Using an inducible lung cancer model, we characterize the changes in intermediary metabolism that occur during CACS in mice. We identify a unique serum metabolite profile consisting of low ketones and increased glucocorticoid levels. Hypoketonemia is associated with reduced expression of hepatic peroxisome proliferator-activated receptor-α (PPARα) targets that regulate fatty acid oxidation and ketogenesis. Replacing ketone production using the PPARα agonist, fenofibrate, reduced glucocorticoid levels, prevented skeletal muscle wasting, and minimized weight loss. These exciting results provide important preclinical data toward a therapeutic strategy. (See pp. E743–E752.)

Linking secondary metabolites to gene clusters through genome sequencing of six diverse *Aspergillus* species

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The genus of *Aspergillus* holds fungi relevant to plant and human pathology, food biotechnology, enzyme production, model organisms, and a selection of extremophiles. Here we present six whole-genome sequences that represent unexplored branches of the *Aspergillus* genus. The comparison of these genomes with previous genomes, coupled with extensive chemical analysis, has allowed us to identify genes for toxins, antibiotics, and anticancer compounds, as well as show that *Aspergillus novofumigatus* is potentially as pathogenic as *Aspergillus fumigatus*, and has an even more diverse set of secreted bioactive compounds. The findings are of interest to industrial biotechnology and basic research, as well as medical and clinical research. (See pp. E753–E761.)

Faulty neuronal determination and cell polarization are reverted by modulating HD early phenotypes

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We report that huntingtin mutation affects specific aspects of human neurodevelopment at the level of neuronal progenitor specification and its early commitment, leading to an abnormal cell organization and acquisition of mature neuronal identities in cerebral organoids. We also show that down-regulation of mutant huntingtin or pharmacological inhibition of one of its effectors, ADAM10, successfully rescues neuronal differentiation, suggesting that an early intervention may revert neurodegeneration later in life. (See pp. E762–E771.)

TRPM4 and TRPM5 are both required for normal signaling in taste receptor cells

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It is currently thought that the transduction of bitter, sweet, and umami stimuli in taste cells depends on G protein-coupled receptor signaling with transient receptor potential melastatin 5 (TRPM5) acting as a common downstream component. However, in the absence of TRPM5, mice have a reduced, but not abolished, ability to detect these stimuli, suggesting that a TRPM5-independent pathway also contributes to taste transduction. Here, we identify a critical role for the TRPM4 channel in the detection of these taste qualities. Deletion of either TRPM4 or TRPM5 impairs sensitivity to bitter, sweet, and umami stimuli, and loss of both TRPM4 and TRPM5 abolishes taste responses to these stimuli. Our results show that both TRPM4 and TRPM5 are required and sufficient for the transduction of bitter, sweet, and umami stimuli. (See pp. E772–E781.)

Structural heterogeneity and intersubject variability of Aβ in familial and sporadic Alzheimer's disease

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An expanding body of evidence argues that the Aβ and tau proteins share important characteristics of prion propagation to cause

pathogenesis in Alzheimer's disease (AD). Aβ and tau form a number of amyloids (β-sheet–rich structures) with distinct conformations ("strains"), some of which give rise to different diseases and associated pathologies. We develop new probes of amyloid structure and use these to identify conformational strains of Aβ in heritable and sporadic forms of AD patient samples. We demonstrate that distinct strains of Aβ can be discerned in different disease types, or in different brain compartments within a given patient. Our findings may potentially explain the spectrum of clinical and pathologic features observed in AD. (See pp. E782–E791.)

Mechanism-specific assay design facilitates the discovery of Nav1.7-selective inhibitors

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Subtype-selective modulation of ion channels is often important, but extremely difficult to achieve for drug development. Using Nav1.7 as an example, we show that this challenge could be attributed to poor design in ion channel assays, which fail to detect most potent and selective compounds and are biased toward nonselective mechanisms. By exploiting different drug binding sites and modes of channel gating, we successfully direct a membrane potential assay toward non–pore-blocking mechanisms and identify Nav1.7-selective compounds. Our mechanistic approach to assay design addresses a significant hurdle in Nav1.7 drug discovery and is applicable to many other ion channels. (See pp. E792–E801.)

From in silico hit to long-acting late-stage preclinical candidate to combat HIV-1 infection

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Nonnucleoside reverse transcriptase inhibitors (NNRTIs) are essential components of highly active antiretroviral therapy; however, concerns about poor pharmacological properties, dose restriction because of toxicity, and drug resistance have limited treatment options. Our computational and structure-guided design studies for lead optimization have transformed a 5 μM virtual screening hit into a class of NNRTIs with remarkable potency, safety, drug resistance profile, and pharmacological properties. We report a representative, compound I, with marked synergy with existing HIV-1 drugs and antiviral efficacy in HIV-1–infected humanized mice. A single dose of long-acting nanoformulation of compound I retains sustained levels and efficacy for ~3 weeks, confirming potential as a late-stage preclinical candidate. Additionally, these properties of compound I suggest that it may be a promising candidate to evaluate for preexposure prophylaxis. (See pp. E802–E811.)

IKKα inactivation promotes Kras-initiated lung adenocarcinoma development through disrupting major redox regulatory pathways

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Reactive oxygen species (ROS) can promote tumorigenesis or kill cancer cells. How different cancer-associated genetic alterations regulate ROS balance and outcome is of great importance for the design of rational cancer treatments, many of which affect ROS metabolism and sensing. Kras activation induces a ROS defense system and cell senescence, which counteract its oncogenic activity. *KRAS*-activating mutations are accompanied by IKKα loss mutations that result in elevated NOX2 but decreased expression of the NRF2 ROS defense system. Thus, IKKα ablation turns the antitumorigenic effect of Kras-induced ROS to a protumorigenic effect that enhances Krasinduced progression of lung adenocarcinoma (ADC). Restoration of IKKα activity or inhibition of the pathways activated on its loss may offer new opportunities for ADC treatment. (See pp. E812–E821.)

Growth is required for perception of water availability to pattern root branches in plants

Neil E. Robbins II and José R. Dinneny

Plant roots activate lateral branching in response to contact with available water, but the mechanism by which this environmental signal is perceived is poorly understood. Through a combination of empirical and mathematical-modeling approaches we discovered a central role of tissue growth in this process. Growth causes water uptake, and the biophysical changes that occur during this process are interpreted by the organism to position new lateral branches. This observation is a significant advancement in our understanding of how the environment shapes plant development and demonstrates that perception of water is intimately tied to a core biological function of the root. (See pp. E822–E831.)

Women live longer than men even during severe famines and epidemics

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Women live longer than men in nearly all populations today. Some research focuses on the biological origins of the female advantage; other research stresses the significance of social factors. We studied male–female survival differences in populations of slaves and populations exposed to severe famines and epidemics. We find that even when mortality was very high, women lived longer on average than men. Most of the female advantage was due to differences in mortality among infants: baby girls were able to survive harsh conditions better than baby boys. These results support the view that the female survival advantage is modulated by a complex interaction of biological environmental and social factors. (See pp. E832–E840.)