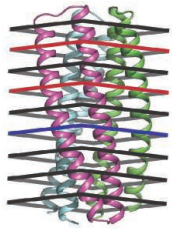
RESEARCH

Designed proteins undergo pH-induced transitions

Boyken et al., *p. 658*



IN *SCIENCE* JOURNALS

Edited by **Stella Hurtley**

DEVELOPMENT

A tale of tadpole tail regeneration

Some vertebrates, including some amphibians, show a remarkable, if sometimes restricted, ability to regenerate lost appendages. Aztekin *et al.* compared naturally occurring regeneration-competent and -incompetent *Xenopus laevis* tadpoles using single-cell messenger RNA sequencing. They identified regeneration-organizing cells (ROCs) that could coordinate tail regeneration. Relocation of ROCs from the body to the amputation plane enabled specialized wound epidermis formation and subsequent regeneration. ROCs simultaneously expressed many different ligands that can induce proliferation of different progenitor cell populations. Thus, by signaling to underlying progenitors, ROCs orchestrate the growth of a new appendage. —BAP

Science, this issue p. 653

Tadpoles of the African clawed frog can sometimes regenerate severed tails.

PROBE MICROSCOPY

Visualizing superexchange interactions

The resolution that can be achieved in scanning probe microscopy can be greatly enhanced by absorbing a molecule such as CO on the probe tip. Czap *et al*. now show that this approach can be used to scan spin and magnetic properties of molecules on a surface. They adsorbed a magnetic molecule, Ni(cyclopentadienyl)$_2$, on a silver surface and then transferred one of these molecules to a scanning tunnel microscope tip. They could then bring the tip toward the adsorbate-covered surface and map out the strength of superexchange interactions. —PDS

Science, this issue p. 670

NEUROSCIENCE

The brain circuits of strategic decisions

Primates can compute and integrate low-level decisions to make strategic adjustments to higher-level decisions. The neural substrates and mechanisms that allow this process are not known. Sarafyazd and Jazayeri performed single-cell recordings in the dorsomedial frontal cortex and the anterior cingulate cortex of monkeys. They observed that the two brain areas, which have been implicated in error monitoring and the control of adaptive behavior, processed signals involved in causal inference. The anterior cingulate acted downstream of the dorsomedial frontal cortex. It used graded evidence derived from errors in low-level processes in a decision hierarchy to select between longer-term behavioral strategies. —PRS

Science, this issue p. 652

NEURODEVELOPMENT

Brain cell transcriptomes in autism

Autism manifests in many ways. Despite that diversity, the disorder seems to affect specific cellular pathways, including those observed in the neocortex of patients' brains. Velmeshev *et al*. analyzed the transcriptomes of single brain cells, including neurons and glia, from patients with autism. Single-nucleus RNA sequencing analysis suggested that affected pathways regulate synapse function as well as neural outgrowth and migration. Furthermore, in patient samples, specific sets of genes enriched in upper-layer projection neurons and microglia correlated with clinical severity. —PJH

Science, this issue p. 685

CHEMICAL STRUCTURE

Dynamical refinement spots a difference

For chiral molecules used in drugs, one isomer can have beneficial bioactivity, whereas the others are useless or even harmful. Determining the absolute configuration of molecules with chiral centers is often achieved through x-ray

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crystallography, but this requires relatively large crystals and high-quality data. Brázda *et al*. used electron diffraction to determine the absolute structure of an extremely radiation-sensitive crystal with micrometer dimensions (see the Perspective by Xu and Zou). In a strategy analogous to serial crystallography methods, many frames were combined to generate a complete dataset. Refinement incorporating dynamical effects differentiated the correct and incorrect molecular configuration. —MAF

Science, this issue p. 667; see also p. 632

MEMBRANE TRANSPORT

Transport control

The membrane protein P-glycoprotein protects cells by using energy from adenosine triphosphate (ATP) hydrolysis to expel chemical substances, including drugs. Inhibiting P-glycoprotein may thus ameliorate drug resistance. Structures of P-glycoprotein in the apo state and bound to substrate and inhibitor give insight into the transport mechanism, but a full picture requires access to substates in the transport cycle. Dastvan *et al*. used double electron electron resonance spectroscopy to show that substrates enhance transport by stabilizing an asymmetric post–ATP-hydrolysis state. By contrast, inhibitors stabilize a symmetric state that impairs transport. —VV

Science, this issue p. 689

CHEMICAL PHYSICS

Bonding's outer limit

In a Rydberg state, an atom has been very nearly, but not quite, ionized. This puts the electron relatively far from the nucleus, and two atoms in such a state can thus form a rather long-range bond. Hollerith *et al*. observed this phenomenon in fine detail by exciting pairs of ultracold rubidium atoms along the diagonal of an optical lattice. The authors resolved the vibrational state structure spectroscopically and showed that the Rydberg dimers manifested bond lengths exceeding 700 nanometers. —JSY

Science, this issue p. 664

CANCER

The secret life of cediranib

Anti-angiogenic agents are used to inhibit the formation of new blood vessels that supply nutrients and oxygen to tumors. However, recent findings suggest that they can have additional anticancer effects. The anti-angiogenic drug cediranib can sensitize tumors to poly(ADP-ribose) polymerase (PARP) inhibitors, which normally target tumors with defective DNA repair. Kaplan *et al*. determined that cediranib damages tumors both by interrupting their blood supply, inducing hypoxia, and by directly affecting pathways involved in DNA repair, sensitizing cancer cells to PARP inhibitors. —YN

Sci. Transl. Med. **11**, eaav4508 (2019).

IMMUNOLOGY

Recall responses by human NK cells

One of the traditional dividing lines separating innate and adaptive immunity is the restriction of immune memory to adaptive immune cells. However, accumulating evidence in animal models has suggested that memory responses can be evoked in natural killer (NK) cells. Nikzad *et al*. asked whether human NK cells also exhibit memory responses. They analyzed NK cells recovered from humanized mice and NK cells found in the viral antigen-challenged skin of adult volunteers who had chickenpox as children. Antigen-specific recall responses by human NK cells were observed in both experimental systems. Thus, human NK memory responses contribute to host protection after vaccinations or natural infections. —IRF

Sci. Immunol. **4**, eaat8116 (2019).

IN OTHER JOURNALS

Edited by **Caroline Ash** *and* **Jesse Smith**

The GRAVITY Collaboration used the Very Large Telescope, located in the Atacama Desert of northern Chile, to observe the star HR 8799 and one of its planets.

PHOTO: G. HÜDEPOHL (ATACAMAPHOTO.COM)/ESO/CC-BY

MUTATION

DNA damage and parental age

Mutations in the sperm and eggs of humans have been attributed to errors in DNA replication. More than 75% of human germline mutations are paternal in origin. This is thought to be a result of male gametes undergoing more rounds of cell division than female gametes and thus having a greater probability of replication error. Gao *et al*. examined datasets of de novo mutations in the human germline and found that the mutation bias is not driven by spermatogenesis. They observed a surprising degree of C-to-G transversions and CpG transitions, indicative of DNA damage. The authors deduced that most mutations in early embryos are more likely to result from factors associated with maternal age at conception and accumulated damage in oocytes and embryos than from replication error. —LMZ

Proc. Natl. Acad. Sci. U.S.A. **116**, 9491 (2019).

KIDNEY DISEASE

A pharmacological hat trick

The number of people with type 2 diabetes (T2D) may reach 510 million by the year 2030, a trend largely driven by the global rise in obesity rates. Because T2D often compromises kidney function, the number of people with kidney failure is also expected to rise dramatically. A new study suggests that a drug already in clinical use for T2D may provide multiple health benefits to such patients. Canagliflozin lowers blood glucose levels by blocking reabsorption of glucose in the kidney. In a large randomized trial of patients with T2D and chronic kidney disease, Perkovic *et al*. found that those receiving canagliflozin were 30% less likely to develop end-stage kidney disease and 20 to 30% less likely to develop cardiovascular disease than those receiving placebo. —PAK

N. Engl. J. Med. 10.1056/NEJMoa1811744 (2019).

ALSO IN *SCIENCE* JOURNALS

Edited by **Stella Hurtley**

CANCER

Supporting tumor suppression

The protein PTEN is a phosphatase and tumor suppressor whose activity is often decreased in human cancers. Thus, reactivating such a protein could potentially be an effective therapy against cancer. Lee *et al*. identified a ubiquitin E3 ligase (WWP1) as a PTEN-interacting protein that modifies PTEN and inhibits its tumor suppressive activity (see the Perspective by Parsons). Depletion of WWP1 increased dimerization and membrane recruitment of PTEN. A natural compound found to be a pharmacological inhibitor of WWP1 inhibited tumor growth in a mouse model of prostate cancer. Thus, reactivation of the tumor suppressor PTEN may provide a strategy for battling tumors. —LBR

Science, this issue p. 651; see also p. 633

METAMATERIALS

Dynamic metasurfaces

Optical metasurfaces have opened an entirely new field in the quest to manipulate light. Optical metasurfaces can locally impart changes to the amplitude, phase, and polarization of propagating waves. To date, most of these metasurfaces have been passive, with the optical properties largely set in the fabrication process. Shaltout *et al*. review recent developments toward time-varying metasurfaces and explore the opportunities that adding dynamic control can offer in terms of actively controlling the flow of light. —ISO

Science, this issue p. 648

CELLULAR NEUROSCIENCE

Local translation in presynaptic terminals

Proteins carry out most of the functions in cells, including neurons, which are one of the most morphologically complex cell types in the body. This poses challenges for how proteins can be supplied to remote regions where connections (synapses) are made with other neurons. One solution to the neuron protein-supply problem involves the local synthesis of proteins from messenger RNA (mRNA) molecules located at or near synapses. Hafner *et al*. used RNA sequencing methods and super-resolution microscopy to show that axon terminals contain hundreds of mRNA molecules as well as the machinery needed for protein synthesis. Furthermore, the axon terminals were able to use these components to make proteins that participate in synaptic transmission. —SMH

Science, this issue p. 650

OUTER SOLAR SYSTEM

New Horizons flies past MU_{69}

After flying past Pluto in 2015, the New Horizons spacecraft shifted course to encounter (486958) 2014 MU_{69}, a much smaller body about 30 kilometers in diameter. MU_{69} is part of the Kuiper Belt, a collection of small icy bodies orbiting in the outer Solar System. Stern *et al*. present the initial results from the New Horizons flyby of MU_{69} on 1 January 2019. MU_{69} consists of two lobes that appear to have merged at low speed, producing a contact binary. This type of Kuiper Belt object is mostly undisturbed since the formation of the Solar System and so will preserve clues about that process. —KTS

Science, this issue p. 649

SUGAR CHEMISTRY

Sweet spot for making oligosaccharides

Sugars pose a challenge for chemists: how to string together functional group–rich building blocks that can adopt multiple conformations. Two papers in this issue used sugar building blocks constrained by a macrocyclic linker to encourage formation of a specific glycosidic linkage (see the Perspective by Pohl). Ikuta *et al*. used glucose building blocks containing a linker that changes the sugar conformation to synthesize cyclic oligomers with only three or four units. The linker changes the conformation of the glucose monomers, enabling them to come together despite the strain in the final structure. Komura *et al*. prepared sialic acid building blocks with a linker that allows for selective formation of the α-anomeric linkage with a range of nucleophiles. They synthesized dimers of sialic acid with many different linkages and a pentamer with four α(2,8) linkages. This method enabled chemical synthesis of components of mammalian glycans involved in brain development, cell adhesion, and immune response. —MAF

Science, this issue p. 674, p. 677; see also p. 631

ORGANIC CHEMISTRY

Excising an olefin

Plants produce an abundance of structurally complex terpene compounds that are useful precursors to pharmaceuticals and other fine chemicals. However, the carbon frameworks of these compounds constrain the available pathways for diversification. Smaligo *et al*. now show that successive treatment with ozone, an iron oxidant, and a hydrogen-atom donor can cleanly cleave pendant olefins from terpenes and related compounds (see the Perspective by Caille). Breaking the bond between saturated and double-bonded carbon centers offers a direct route to desirable chiral intermediates from readily available, inexpensive precursors. —JSY

Science, this issue p. 681; see also p. 635

AUDITORY NEUROSCIENCE

Machine learning improves hearing aids

A key challenge in improving assistive hearing devices is isolating and separating different voices in noisy or crowded settings. This task is especially difficult without prior exposure to the voices of interest and without knowing which voice to amplify. Han *et al*. used deep attractor networks—a powerful machine-learning technique—to project unfamiliar mixed audio signals into a high-dimensional space to separate signals from independent speakers. Comparing these separated sources with auditory cortical responses of a user allowed the method to determine and amplify the attended voice. The approach was as accurate as methods trained with clean audio sources and may thus enable hearing-impaired users to communicate more naturally in complex social environments. —AC and KJP

Sci. Adv. 10.1126/sciadv.aav6134 (2019).

INFLAMMASOMES

BCAPing inflammasome activation

The phosphoinositide 3-kinase adaptor protein BCAP (B cell adapter for PI 3-kinase) limits macrophage responses to stimulation of Toll-like receptors. Inflammasomes are multiprotein complexes that activate the protease caspase-1 to process the proinflammatory cytokine interleukin-1β (IL-1β). Carpentier *et al*. identified a distinct role for BCAP in preventing excessive activation of inflammasomes. In macrophages, BCAP reduced active caspase-1 levels, IL-1β release, and cell death after exposure to the toxin nigericin or after bacterial infection. BCAP delayed caspase-1 activation by inflammasomes, and loss of BCAP

promoted bacterial clearance in mice. —ERW

Sci. Signal. **12**, eaau0615 (2019).

PROTEIN DESIGN

Designed to respond

Protein design has achieved success in finding sequences that fold to very stable target structures. Protein function, however, often requires conformational dynamics. Boyken *et al*. describe designed proteins that undergo conformational transitions in response to pH. They designed helical oligomers in which histidines are positioned in hydrogen-bond networks at the interfaces, with complimentary hydrophobic packing around the networks. Lowering the pH protonated the histidine, disrupting the oligomers. After endocytosis into low-pH compartments in cells, the designed proteins disrupted endosomal membranes. —VV

Science, this issue p. 658

AGING

Agents for healthful aging

During aging, senescent cells—dysfunctional noncycling cells—accumulate. This accumulation is associated with numerous diseases, including osteoarthritis and cancer. In a Perspective, van Deursen discusses the preclinical evidence from mice showing that selectively eliminating senescent cells using targeted senolytic drugs can improve longevity and prevent or reduce age-associated disease. Such drugs are now moving into clinical trials, but we still need to understand much more about senescent cells. —GKA

Science, this issue p. 636