al. sent 50 indistinguishable single-mode squeezed states into a 100-mode ultralow-loss interferometer and sampled the output using 100 high-efficiency single-photon detectors. By obtaining up to 76-photon coincidence, yielding a state space dimension of about 10^{30}, they measured a sampling rate that is about 10^{14}-fold faster than using state-of-the-art classical simulation strategies and supercomputers. —ISO

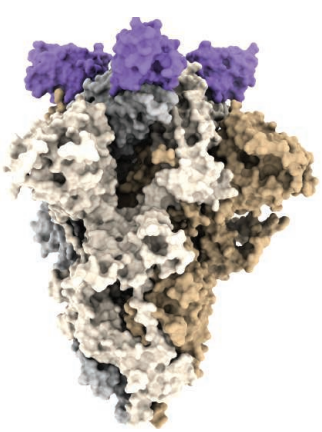
Science, this issue p. 1460

CORONAVIRUS

Nanobodies that neutralize

Monoclonal antibodies that bind to the spike protein of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) show therapeutic promise but must be produced in mammalian cells and need to be delivered intravenously. By contrast, single-domain antibodies called nanobodies can be produced in bacteria or yeast, and their stability may enable aerosol delivery. Two papers now report nanobodies that bind tightly to spike and efficiently neutralize SARS-CoV-2 in cells. Schoof *et al.* screened a yeast surface display of synthetic nanobodies and Xiang *et al.* screened anti-spike nanobodies produced by a llama. Both groups identified highly potent nanobodies that lock the spike protein in an inactive conformation. Multivalent constructs of selected nanobodies achieved even more potent neutralization. —VV

Science, this issue p. 1473, p. 1479



The SARS-CoV-2 spike protein bound to three copies of a neutralizing nanobody (purple)

CREDITS: (LEFT) SCHOOF *ET AL.*; (RIGHT) BSIP/UIG/GETTY IMAGES

DIRECTED EVOLUTION

Two steps forward—now look back

Whether designed computationally or uncovered in activity screening, enzymes repurposed for biocatalysis rarely start at the peak of proficiency. However, directed evolution can in some cases increase catalytic efficiency of a poor enzyme by many orders of magnitude. Otten *et al.* used a suite of biochemical techniques to investigate the origins of rate enhancement in a previously evolved model enzyme. Two conformational states are present in the initial, computationally designed enzyme, but only one is active. Shifting the population toward the active state is one factor in increasing catalytic efficiency during evolution. Single mutations do not greatly increase activity, but the synergistic combination of just two out of 17 substitutions can provide most of the rate enhancement seen in the final, evolved enzyme. —MAF

Science, this issue p. 1442

BIOSENSORS

Form, fit, and function

Improper fit between the prosthetic socket and the residual limb of persons with amputation causes discomfort, pressure ulcers, and altered load bearing. Kwak *et al.* developed pressure and temperature sensors to monitor the interface between a prosthesis and residual limb. The soft sensors communicated wirelessly with portable electronic devices during walking, sitting, and standing in nonamputees wearing prosthesis simulators and in two individuals with transtibial and transfemoral amputations. —CC

Sci. Transl. Med. **12**, eabc4327 (2020).

IN OTHER JOURNALS

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

SIGNAL TRANSDUCTION

An anti-arthritis signal

A signaling connection that allows transforming growth factor–β (TGF-β) to protect cartilage from osteoarthritis could guide new therapeutic strategies. Expression of the transcription factor FoxO1 in cartilage decreases with aging. Loss of FoxO family members causes osteoarthritis-like damage in mice and humans. Wang *et al.* found that TGF-β specifically promotes expression of the FoxO1 isoform in isolated mouse chondrocytes in a manner that depends on activation of TGF-β–activated kinase 1 (TAK1). Overexpression of FoxO1 in mice protected against experimentally induced arthritis. The protective TGF-β/TAK1 signaling nexus appeared to act, at least in part, by activating autophagy. —LBR *Proc. Natl. Acad. Sci. U.S.A.* **117**, 30488 (2020).

Expression of the transcription factor FoxO1 in cartilage decreases with aging, causing osteoarthritis-like damage in mice and humans.

IMMUNOGENOMICS

Phenotyping population transcriptomes

Molecular phenotypes, such as the level of RNAs required for cell- or tissue-specific gene expression, are useful for discerning the function of genetic variants. Bonaguro *et al.* examined previously collected transcriptional cohorts and investigated expression of the gene *CRELD1*, known to be important for human heart development. They found that

NEURODEVELOPMENT

Synapse formation in the visual cortex

Synapses between neurons depend on cell-adhesion molecules for their formation. In the visual cortex, synapses are built and refined in response to visual experience. Nectin-3, one of a group of immunoglobulin superfamily cell-adhesion molecules, can shake hands with its binding partner nectin-1 across the synaptic cleft to stabilize a developing synapse. Inferring synapse numbers from dendritic spine density, Tomorsky *et al.* studied the function of nectin-3 in the development of the mouse visual cortex. In normal development, the number of dendritic spines increases once neonatal mice open their eyes. The authors found that overexpression of nectin-3 locked in too much stability and that not enough new dendritic spines formed for normal neural migration. Underexpression of nectin-3 allowed too many new dendritic spines to form, which was also harmful to ocular development. As in much of life, somewhere precisely in between seems to work best. —PJH *Neural Dev.* **15**, 13 (2020).

Neonatal mouse pups require just the right amount of nectin-3, an immunoglobulin superfamily cell-adhesion molecule, to ensure normal eye development.

this gene is expressed throughout adult human and mouse tissues. Focusing on immune system cell populations, they identified variation in *CRELD1* gene expression in humans. Inactivation of *Creld1* in mice led to reduced T cell populations and loss of WNT signaling, which was also seen in humans with low levels of *CRELD1* expression in their T cells. Thus, variation in gene expression provides a molecular phenotype that can be informative for investigating cell- and tissue-specific gene function. —LMZ

Nat. Immunol. **21**, 1517 (2020).

LIPID HOMEOSTASIS

SURF4 lipid carrier proteins

Infants with a rare inherited disorder called chylomicron retention disease suffer from severe fat malabsorption. Disease is caused by a retention of lipid carrier proteins resulting from mutations in a protein called SAR1B, which decorates intracellular protein-containing packages. In a recent study, Wang *et al.* discovered how cells in the liver distinguish lipid carrier proteins from other protein cargos. A second protein called SURF4 recognizes and selects the lipid carrier proteins by acting as their designated cargo receptor. SAR1B and SURF4 work together to ensure delivery of the packages to the cell's membrane for secretion. These findings could provide targets for the treatment of dyslipidemia and atherosclerosis, as well as chylomicron retention disease. —DJ

Cell Metab. 10.1016/j.cmet.2020.10.020 (2020).

GRAVITATION

Gravitational redshift of the Sun

General relativity predicts that light emitted from a massive body is redshifted by its gravitational field. This gravitational redshift effect has previously been verified using white dwarfs and terrestrial experiments. Measuring it for the Sun is complicated by the motions of plasma on the surface, which Doppler-shift spectral lines by amounts similar to that of the predicted signal. González Hernández *et al.* analyzed a high-resolution spectrum of sunlight reflected off the Moon, thereby averaging over the solar disc, calibrated using a laser frequency comb. After compensating for plasma motions, they measured a gravitational redshift that is consistent with general relativity, within the uncertainty of 1 to 2%. —KTS

Astron. Astrophys. **643**, A146 (2020).

QUANTUM INFORMATION

Accepting imperfection

Quantum computers are capable, at least in theory, of performing calculations out of the reach of classical computers. Proving that in practice is, however, not straightforward; estimates for how long it would take a classical (super)computer to complete a calculation can vary widely. Those estimates typically rest on the use of classical computers to simulate an idealized quantum computer: one that does not suffer from decoherence. Zhou *et al.* show that if the imperfections of current quantum hardware are taken into account, then classical computers become much more competitive. The results suggest that increasing the fidelity of quantum gates is a more viable approach to improving the performance of quantum computers than increasing the number of qubits. —JS

Phys. Rev. X **10**, 041038 (2020).

CHEMICAL BIOLOGY

Bright prospects for molecular glues

Protein-protein interactions (PPIs) are crucial to cellular functions such as signaling, protein degradation, and cellular transport. There is currently great interest in small molecules, which can stabilize transient or non-native interactions and thus alter the proteome or state of the cell. Sijbesma *et al.* adapted a method using fluorescence anisotropy to enable screening for stabilization of a PPI between a phosphopeptide-binding protein and a known weak binding partner peptide. Screening a panel of thiols covalently attached to a cysteine on the peptide revealed several fragments that led to a fivefold increase in affinity for the complex. —MAF

ACS Chem. Biol. 10.1021/acschembio.0c00646 (2020).

Synapse formation in the visual cortex

Pamela J. Hines

Science **370** (6523), 1429-1430.
DOI: 10.1126/science.370.6523.1429-c