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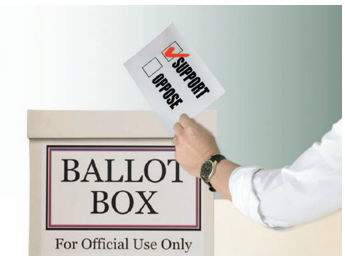
PSYCHOLOGY

The subtle influence of where people vote

Can the polling location where people vote affect how they vote? During voting in U.S. elections, the right to free speech is temporarily and selectively curtailed: signage and amplified sounds are prohibited near polling locations, which include schools and churches. The government justifies the restrictions by citing the greater importance of enabling citizens to vote freely. But, as Jonah Berger *et al.* report, where people vote—i.e., the polling location itself—can influence the choices they make. The authors examined the 2000 Arizona general election, in which a ballot initiative proposed raising the state sales tax from 5.0% to 5.6% to increase education funding. After controlling for political preferences, the authors found that citizens were significantly more likely to support the initiative if they voted in a school. In a subsequent experiment, subjects exposed to images of schools, such as lockers and classrooms, were more likely to support a hypothetical tax increase to fund public schools than were subjects exposed to images of office buildings. Environmental stimuli in a location can "prime" memory, activating societal norms or features of a person's self-concept and thus influencing their choices and actions, according to the authors. — K.M.



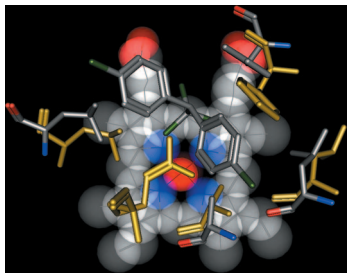
Polling location has a subtle influence on voter choice.

"Contextual priming: Where people vote affects how they vote" by Jonah Berger, Marc Meredith, and S. Christian Wheeler (see pages 8846–8849)

BIOCHEMISTRY

The secret of DDT-resistant mosquitoes

Since the introduction of DDT as an insecticide, several strains of mosquito have evolved and developed resistance to the compound. In resistant insects, DNA microarray studies have pinpointed a number of upregulated cytochrome P450 genes. Ting-Lan Chiu *et al.* modeled the catalytic site geometries of two *Anopheles gambiae* P450s that appear strongly linked to DDT resistance, finding that one, CYP6Z1, seems to have a site geometry well matched to DDT. *In vitro* metabolic experiments confirmed the modeling results. The authors report that both CYP6Z1 and CYP6Z2 P450s are overexpressed in resistant mosquitoes collected in West and East Africa, as evidenced by homology models based on sequence alignments with CYP3A4 (the major drug-metabolizing P450 in humans). The authors used the MOE software suite to optimize these models and to dock two insecticide molecules (DDT and carbaryl) and a plant toxin (xanthotoxin) within the catalytic cavities. Based on these predictive models, the protein backbones appear virtually identical, but three extended side chains in CYP6Z2 make the DDT binding energy prohibitively high. Chiu *et al.* conclude that increased CYP6Z1 expression likely enables DDT resistance. These structural predictions should facilitate the search for CYP6Z1 inhibitors that can synergize with current insecticides, making them more effective, the authors say. — K.M.



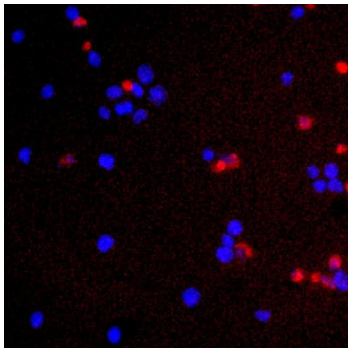
The *Anopheles gambiae* CYP6Z1 catalytic site can metabolize DDT.

"Comparative molecular modeling of Anopheles gambiae *CYP6Z1, a mosquito P450 capable of metabolizing DDT" by Ting-Lan Chiu, Zhimou Wen, Sanjeewa G. Rupasinghe, and Mary A. Schuler* (see pages 8855–8860)

MEDICAL SCIENCES

Picking your cancer poison

Topoisomerase poisons target topoisomerase enzymes and interfere with the unwinding of DNA for transcription; for these reasons, they are widely used and effective chemotherapeutic agents. Tumors, however, are often insensitive to, or become resistant to, these drugs, and the genetic basis for this resistance is unclear. To identify genetic factors involved in response to doxorubicin (a front-line chemotherapy agent that targets topoisomerase 2), Darren Burgess *et al.* screened a library of shRNAs—molecules that knock down expression of target



shTop2A cells show attenuation of doxorubicin-induced apoptosis.

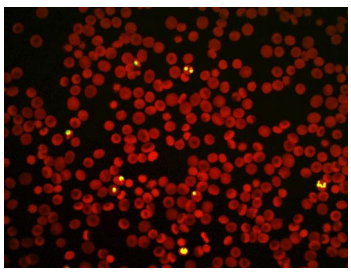
genes—in lymphoma cells. They found that shRNAs targeting topoisomerase 2α (*Top2A*) frequently confer resistance to the drug. Mice injected with *Top2A*-deficient lymphoma cells and then treated with doxorubicin exhibited resistance to the drug, fewer tumors, and longer overall survival. Mice with a knockdown of topoisomerase 1 (*Top1*) showed resistance to camptothecin, a topoisomerase 1 poison. Unexpectedly, *Top1* knockdown hypersensitized cells to topoisomerase 2 poisons, suggesting a synergy between *Top1* suppression and topoisomerase 2 poisoning. The authors say that their results point to an approach for validating candidate genes and screening for other genetic determinants of drug resistance, and they suggest that levels of topoisomerase enzymes might serve as biomarkers to guide the clinical use of topoisomerase poisons. — M.M.

"Topoisomerase levels determine chemotherapy response in vitro *and* in vivo*" by Darren J. Burgess, Jason Doles, Lars Zender, Wen Xue, Beicong Ma, W. Richard McCombie, Gregory J. Hannon, Scott W. Lowe, and Michael T. Hemann* (see pages 9053–9058)

MICROBIOLOGY, CHEMISTRY

Combining chemical and computer screening

New drugs are always needed in the fight against malaria. David Plouffe *et al.* report on a chemical- and computer-based screening method that can find new drug candidates and identify the pathways on which antimalarial compounds work. The authors tested ≈1.7 million compounds in a 1,536-well cell-based screen and identified ≈6,000 compounds with potent antimalarial activity. In addition to picking up most known antimalarial compounds—validating their screening method—the authors identified >530 distinct chemical scaffolds among their candidates. They then used historical screening data to determine the probable mechanism of action of some of the candidates. The screening process used data from previous cellular, biochemical, and genomic screens, along with the guilt-by-association principle, to identify the pathway or protein target affected. Both known and unknown targets appeared in their final results. The authors say their technique has the potential to speed the drug discovery process and provide leads for new drugs and pathways for more detailed studies. — P.D.



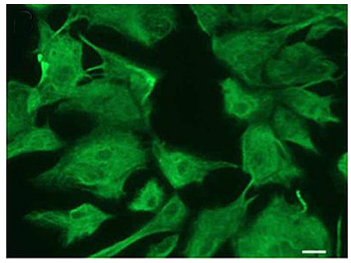
Plasmodium falciparum-infected blood cells. Parasites are shown in yellow.

"In silico activity profiling reveals the mechanism of action of antimalarials discovered in a high-throughput screen" by David Plouffe, Achim Brinker, Case McNamara, Kerstin Henson, Nobutaka Kato, Kelli Kuhen, Advait Nagle, Francisco Adrián, Jason T. Matzen, Paul Anderson, Tae-gyu Nam, Nathanael S. Gray, Arnab Chatterjee, Jeff Janes, S. Frank Yan, Richard Trager, Jeremy S. Caldwell, Peter G. Schultz, Yingyao Zhou, and Elizabeth A. Winzeler (see pages 9059–9064)

PHYSIOLOGY

Hormone-secreting neurons protect against prostate cancer

A set of hormone-secreting nerve cells in the hypothalamus, called β-endorphin-producing (BEP) neurons, are known to play a role in stress regulation and immune function and may also affect tumor progression. Previous research has shown that too few, or inactive BEP neurons are associated with depression, schizophrenia, obesity, and cancer. Dipak Sarkar *et al.* examined the hypothesis that BEP neurons help inhibit tumor growth. The authors used pituitary adenylate cyclase-activating peptide (PACAP)—a cAMP-activating agent—and dbcAMP—a cAMP analog—to differentiate rat neural stem cells from the hypothalamus into BEP neurons, which were later transplanted into the brains of live rats. They then studied tumor growth in the rats that had been given carcinogens to induce prostate tumors. The BEP neurons boosted immune function by increasing natural killer cell activity and reduced inflammation by raising cytokine IFN-γ and lowering cytokine TNF-α. These effects, according to the authors, combined to slow the progression of the prostate cancer. — B.T.



Immunofluorescence staining of nestin in the early stages of differentiation.

"Cyclic adenosine monophosphate differentiated β-endorphin neurons promote immune function and prevent prostate cancer growth" by Dipak K. Sarkar, Nadka I. Boyadjieva, Cui Ping Chen, María Ortigüela, Kenneth Reuhl, E. Michael Clement, Peter Kuhn, and Jason Marano (see pages 9105–9110)