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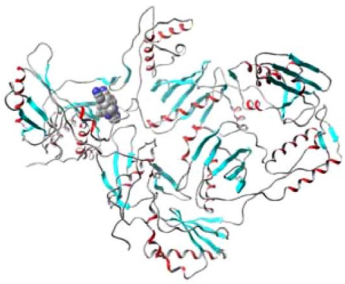
In This Issue

BIOCHEMISTRY

Flexible molecules key to drug resistance

High-resolution crystal structures showing the molecular embrace of a drug called TMC278 have revealed why the molecule is able to combat both wild-type and drug-resistant forms of HIV-1. X-ray images show that TMC278, which was designed to be flexible, bends to accommodate mutations in the binding pocket of reverse transcriptase. Kalyan Das *et al.* engineered two mutant versions of reverse transcriptase, each with two mutations—K103N/Y181C and L100I/K103N—and demonstrate how TMC278 inhibits the mutant forms of reverse transcriptase by flexing and repositioning to fill the binding pockets. The authors report that TMC278 at low doses is highly effective in treating wild-type and drug-resistant forms of HIV-1 and suggest that flexible inhibitors may be an effective method for fighting drug-resistant infections. — B.T.



High-resolution image of wild-type HIV-1.

"High-resolution structures of HIV-1 reverse transcriptase/TMC278 complexes: Strategic flexibility explains potency against resistance mutations" by Kalyan Das, Joseph D. Bauman, Arthur D. Clark, Jr., Yulia V. Frenkel, Paul J. Lewi, Aaron J. Shatkin, Stephen H. Hughes, and Eddy Arnold (see pages 1466–1471)

GENETICS

New role for tiny transcripts

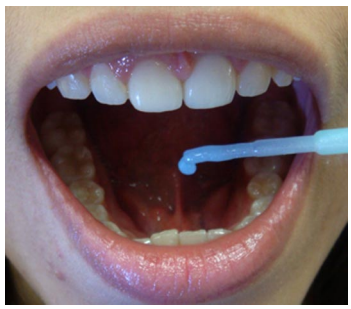
MicroRNAs, snippets of genomic sequence once regarded as junk, are now known for their ability to suppress gene expression by either blocking translation or inducing degradation of target messenger RNA. But these short, single-stranded bits of RNA (21–23 nucleotides long) might be more multitalented than previously thought. Robert Place *et al.* describe a new, somewhat paradoxical, role for microRNAs in boosting gene expression. The authors identified a potential target site for a known microRNA, miR-373, in the promoter region of the gene encoding E-cadherin. They found that inserting miR-373 and its precursor into cultured cells induced expression of E-cadherin and of another gene, called cold shock domain-containing protein C2 (CSDC2), which also contains a putative target site in its promoter. Place *et al.* noted that insertion of miR-373 increased the amount of an enzyme responsible for initiating transcription (RNA polymerase II) at promoters for both genes, supporting a role for microRNAs in inducing gene expression. Given the suspected roles for microRNAs in cancer, the authors suggest that their findings may offer insight into how these tiny molecules affect the expression of genes involved in human disease. — M.M.

"MicroRNA-373 induces expression of genes with complementary promoter sequences" by Robert F. Place, Long-Cheng Li, Deepa Pookot, Emily J. Noonan, and Rajvir Dahiya (see pages 1608–1613)

IMMUNOLOGY

Flu may take a licking

Delivering vaccines directly to the mucosal surfaces can enhance immunity and guard against pathogens at their entry point. Joo-Hye Song *et al.* report a method for administering influenza vaccine under the tongue. Sublingual vaccination is an attractive approach because, in addition to negating the need for injections, the route does not subject the vaccine to degradation in the gastrointestinal tract. Song *et al.* tested the method in mice, finding that two doses of either live or inactivated flu virus conferred protection against infection. The vaccination primed antibody defenses in the respiratory tract and increased antiviral activity in the immune system. In addition, the sublingual route did not allow viruses to travel into the central nervous system, a rare but po-



Human trial of sublingual vaccination.

tentially harmful complication of intranasal vaccination. The authors suggest that, with further testing, administering influenza vaccines under the tongue could be a powerful way to protect against flu and possible pandemics. — T.H.D.

"Sublingual vaccination with influenza virus protects mice against lethal viral infection" by Joo-Hye Song, Huan H. Nguyen, Nicolas Cuburu, Taisuke Horimoto, Sung-Youl Ko, Se-Ho Park, Cecil Czerkinsky, and Mi-Na Kweon (see pages 1644–1649)

MEDICAL SCIENCES

Transcription factor suppresses skin cancer

By the end of 2007, nearly 1 million new cases of melanoma and nonmelanoma skin cancer will be diagnosed in the United States. Activating transcription factor-2 (ATF2), which plays a role in both stress and DNA damage responses, has been implicated in melanoma development and progression. Anindita Bhoumik *et al.* demonstrated that ATF2 protects skin cells from the formation of nonmalignant skin tumors by replacing functional ATF2 with a nonfunctional mutant in mouse keratinocytes, the cells that form the epidermis. After chemically inducing skin cancer in the animals, the authors found that mice lacking transcriptionally active ATF2 showed significant increases in the frequency and number of papillomas. ATF2 regulation of presenilin 1, a highly conserved transmembrane protease, mediated this suppressor activity in the skin. The authors found that squamous and basal cell carcinoma samples from skin cancer patients had reduced nuclear levels of the transcription factor, whereas metastatic melanoma exhibited the opposite, with ATF2 primarily in the nucleus. Decreased nuclear localization of the protein in tumor cells coincides with poor prognosis. The protein had been implicated as an oncogene in metastatic melanoma. The authors suggest that the revelation of ATF2's tumor suppressor role may aid in the development of skin cancer therapeutics. — F.A.

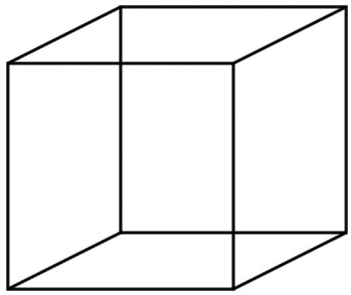
Disruption of ATF2 in mouse skin increases papilloma formation.

"Suppressor role of activating transcription factor 2 (ATF2) in skin cancer" by Anindita Bhoumik, Boris Fichtman, Charles DeRossi, Wolfgang Breitwieser, Harriet M. Kluger, Sean Davis, Antonio Subtil, Paul Meltzer, Stan Krajewski, Nic Jones, and Ze'ev Ronai (see pages 1674–1679)

NEUROSCIENCE

Pupil dilation and perceptual rivalry

How the brain constructs a perception from often-ambiguous external stimuli is largely a mystery. What is known is that the brain receives stimuli in a continuous stream and processes each object, image, and sound more than once. The brain constantly updates each interpretation, switching between various alternatives, in a process called "perceptual rivalry." Using ambiguous stimuli such as the wire-frame drawing known as the Necker cube, Wolfgang Einhäuser *et al.* investigated how individuals switch between various interpretations when a stimulus remains constant. The authors studied the relationship between pupil diameter and perceptual switch, finding that a dramatic increase in pupil diameter coincides with a perceptual switch. They show that the magnitude of dilation is a reliable predictor of the stability or duration of each perception. Einhäuser *et al.* note that norepinephrine plays a critical role in perceptual rivalry and that pupil dilation is driven primarily by norepinephrine released from the locus coeruleus. — B.T.



The Necker cube.

"Pupil dilation reflects perceptual selection and predicts subsequent stability in perceptual rivalry" by Wolfgang Einhäuser, James Stout, Christof Koch, and Olivia Carter (see pages 1704–1709)