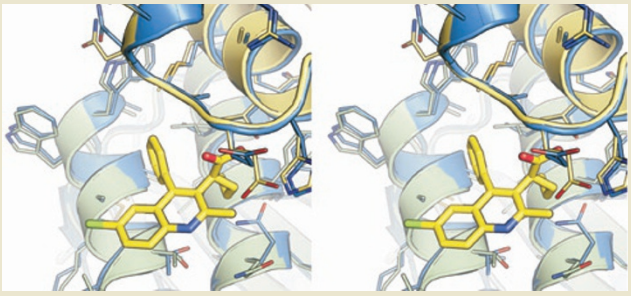
HIV-host interaction inhibitor

Whereas most antiviral drugs target viral enzymes, such as proteases, integrases or reverse transcriptases, the necessity of host co-factors in viral infection and replication means that the latter also offer targets for drug development. Christ *et al.* rationally designed an inhibitor that disrupts the binding of the HIV integrase to the LEDGF/p75 transcriptional co-activator, which mediates chromatin binding of the integrase. Using structural information, the authors performed an *in silico* screen of 200,000 compounds, and selected and experimentally optimized the most promising hits. Their lead compound efficiently inhibited viral replication *in vitro*, but only moderately affected the catalytic activity of the integrase. Co-crystals corroborated binding of the inhibitor to the LEDGF/p75 binding pocket in integrase. No inhibition of the binding of LEDGF/p75 to its cellular targets was observed, consistent with the lack of overt toxicity in cell culture. The molecule did not show significant cross-resistance with any anti-HIV drugs tested, including integrase inhibitors. Virus strains resistant to the new antiviral molecule retained susceptibility to azidothymidine (AZT) and the integrase inhibitor raltegravir, as expected from the different modes of action. (*Nat. Chem. Biol.* **6**, 442–448, 2010) *ME*



Soil metagenome fuels discovery

Many microbes in the soil cannot be cultured in the laboratory, which means that their genes have not been experimentally tested for useful functions. Sommer *et al.* bypass the culturing step by creating libraries of 40- to 50-kb DNA fragments directly from DNA isolated from soil samples. Instead of sequencing the DNA fragments, which is the route taken by traditional 'metagenomics' studies, Sommer *et al.* introduce them into *Escherichia coli* and screen the modified microbes for beneficial traits conferred by genes encoded by the foreign DNA. The researchers use this approach to identify three genes that confer resistance to the toxic by-products syringaldehyde and 2-fuoric acid, which are generated during the conversion of biomass to fuels. In contrast to existing approaches for microbial engineering that involve optimizing a microbe's own genes or adding genes from existing libraries of well-characterized genetic 'parts', this approach, based on screening of metagenomic libraries, provides a means of rapidly identifying completely new genes with desirable functions. (*Mol. Syst. Biol.* **6**, 360, 2010) *CM*

Written by Kathy Aschheim, Laura DeFrancesco, Markus Elsner, Peter Hare & Craig Mak

Rapidly turning over histones

Chromatin assembly and reassembly are essential in regulating gene expression and DNA replication, but a facile method for measuring turnover of chromatin-associated proteins has not been available. Deal *et al.* now describe a technique for doing this, dubbed CATCH-IT for covalent attachment of tags to capture histones and identify turnover. Cells are pulsed with a methionine analog, azidohomoalanine, which can be tagged with biotin by means of an addition reaction with a thiol group. Subsequent passage of isolated and labeled histones on streptavidin affinity columns enables the readout of genome-wide DNA sequences bound up in the newly synthesized histones using tiling arrays. Pulse-chase experiments show that turnover rates are dependent on gene expression levels and further reveal that epigenetic regulatory elements and replication origins are associated with rapid turnover of histones. The researchers measure histone half-lives on the order of 1 to 1.5 hours, far shorter than the cell cycle (~20 h). The fact that histones associated with epigenetically regulated genes are turned over more rapidly than the cell suggests that at least some histone modifications may not be preserved throughout cell division. This brings into question their role in maintaining epigenetic marks. (*Science* **328**, 1161–1164, 2010) *LD*

Recellularized liver grafts

The frequency of liver transplantation, the only effective treatment for hepatic failure, is limited not only by the scarcity of organ donations but also by the large number of donated livers that are unsuitable for transplantation. Uygen *et al.* report compelling progress towards taking full advantage of these otherwise discarded organs. In a refinement of an approach used to engineer replacement hearts, they flush cells out of the structural extracellular matrix of the liver, retaining the three-dimensional structure of the organ and its complex microvasculature. They then repopulate the intricate structural framework with hepatocytes, using portal vein perfusion recirculation. The rejuvenated tissue functions for up to 10 days in culture, as reflected in assays of albumin secretion, urea synthesis and expression of cytochrome P450. Grafts connected to the circulation of live rats support normal liver activity for several hours. Although reconstructing a fully functional liver from the scaffold left by decellularization will require inclusion of the nonparenchymal cells (e.g., sinusoidal endothelial cells, stellate cells, biliary epithelial cells and Kupffer cells), the report provides a strong foundation for efforts to extend the technology to victims of liver disease, which annually claims ~27,000 lives in the United States alone. (*Nat. Med.*, published online 13 June 2010; doi: 10.1038/nm.2170) *PH*

Antimalaria compound libraries

Malaria research has received a fresh infusion of ideas with the publication of two large screens for compounds that kill *Plasmodium falciparum*, the most deadly of the five *Plasmodium* species known to cause malaria in humans. The two reports are noteworthy not only for the large number of hits identified, some of which may lead to new antimalarial drugs, but for the authors' decisions to make their chemical libraries public so as to accelerate drug development by the entire malaria scientific community. Although drug cocktails based on artemisinin now provide effective first-line therapy for malaria around the world, the emergence of resistance to these and previous drugs requires continued research into novel antiparasitic strategies. Of particular interest, many of the hits discovered in the two screens correspond to new targets, including *Plasmodium* kinases. (*Nature* **465**, 305–310, 311–315, 2010) *KA*