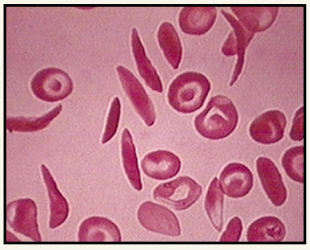
Less sickly blood cells



Researchers first identified the molecular basis of the inherited disorder sickle-cell disease (SCD) over 40 years ago, but so far no effective genetic therapy has been found and treatment options are limited. Now, Philippe Leboulch and a team of scientists at Harvard Medical School and the Massachusetts Institute of Technology (Cambridge, MA) have taken the first major step toward developing such a therapy (*Science* 294, 2368–2371, 2001). SCD is caused by a mutation in the β^A-globin gene that makes the encoded protein sticky and distorts red blood cells into the characteristic sickle shape. Leboulch used an HIV vector, engineered to specifically target stem cells in bone marrow, to replace the mutated globin gene with a healthy copy. The replacement gene—$\beta^{A\text{-}t87q}$-globin—was created by combining parts of the β^A-globin with those of the γ-globin gene, creating a hybrid with enhanced anti-sickling properties. In SCD mice receiving this gene therapy, 99% of red blood cells expressed the healthy globin protein for up to 10 months, and the mice showed none of the associated health complications. The next challenge is to develop a means to knock out the stem cells in bone marrow, which would otherwise continue to generate sick cells. *CM*

Double trouble for yeast genes

Almost 80% of the predicted 6,000 yeast genes are labeled as nonessential, because knockouts have little obvious impact on the yeast's phenotype. To elucidate the function of these "mystery" genes, Charles Boone and colleagues at the University of Toronto (Ontario, Canada) have developed a means of systematically studying the functional relationships of such genes within defined cellular functions (*Science* **294**, 2364–2368, 2001). First, a strain of yeast is created bearing a mutation in the gene of interest, the so-called "query" gene. Next, the yeast is mated with an array of 4,700 yeast strains, each with a distinct gene deletion. Provided that the two strains do not have mutations within the identical gene, mating allows recombination of the genomes, leading to double-mutant progeny. In their study, the researchers looked specifically for gene combinations that influenced cell growth: if both genes were recruited within the same cellular pathway, their disruption resulted in impaired yeast growth. Using this approach (termed systematic genetic analysis, or SGA), the researchers noted 291 functional interactions among 204 genes, creating a valuable functional gene map for yeast. The authors suggest that around 300 SGA screens, and some shrewdly chosen query genes, could be used to create an "effective working genetic scaffold" of the yeast genome. *LF*

Research News Briefs written by Aaron Bouchie, Liz Fletcher, and Christopher Martino.

DNA nanorobotics

By harnessing the kinetic capabilities of biological molecules, such as DNA, researchers hope to lay the foundations for developing "robots" at the nanoscale. For assemblies of DNA, however, the difficulty of controlling and localizing conformational changes triggered in the structure have limited progress. Alterations in temperature or redox potential, for example, result in global changes in the molecules' conformation. Now, researchers at New York University (NY) have used pairs of DNA helices to build an assembly that can undergo robust conformational changes in discrete areas (*Nature* **415**, 62–65, 2002). The researchers created the assembly from aligned pairs of DNA helices, which can be switched between two topologies by the addition of short oligonucleotides known as "set" and "fuel" strands. The two conformations are PX DNA, in which the helical backbones "cross over" at every point they meet, and a topoisomer, JX_2 DNA, in which the crossing over is missing at two sites, resulting in a 180° rotation. The switch between the PX and JX_2 states is triggered by fishing out the "set" strand and adding a "fuel" strand in alternating cycles. Using this strategy, the researchers engineered complex multiconformational DNA assemblies, with different points able to rotate in response to unique "set" and "fuel" sequences. Lead author Nadrian Seeman says that his next project is to incorporate the nanomechanical device into an array that can build small objects in an assembly-line fashion. *AB*

Gone fishing . . . for proteins

The German biotechnology company Cellzome (Heidelberg, German), in conjunction with researchers at the European Molecular Biology Laboratory, has published the first map of the yeast proteome by systematically "fishing out" and identifying native protein complexes (*Nature* **415**, 141–147, 2002). The first of its kind, the map describes the function and interactions of 1,440 yeast proteins comprising 232 multiprotein complexes. Cellzome used homologous recombination to label 1,739 yeast genes with a tag, which was later used to hook out the encoded proteins (and their fellow proteins) from the cellular soup. The component proteins in each complex were then identified using sensitive mass spectroscopy, and a map of protein–protein interactions created. Using the technique, the researchers propose new cellular roles for 344 proteins and identified the functions of a further 231 proteins, suggesting that proteins are much more promiscuous in their associations than was previously thought. Greater insight into the networks of proteins that underlie cellular processes could provide a "more reasoned and informed approach to drug discovery," say the authors. In particular, understanding how drugs act on complexes of proteins, rather than single proteins, could better anticipate drug efficacy and side effects and could be useful in lead drug selection. The yeast proteome map is available at http://yeast.cellzome.com. *LF*

Microbial taste for PCBs

Researchers at the Center of Marine Biotechnology at the University of Maryland Biotechnology Institute have identified the first microbe capable of dechlorinating one of the most intransigent classes of pollutants, polychlorinated biphenyls (PCBs), under anaerobic conditions. Although researchers know that anaerobic bacteria can dechlorinate PCBs, such microorganisms have been difficult to identify and to culture. From the sediment in Baltimore harbour, Harold May and colleagues used DNA fingerprinting and cloning to identify a microbe, dubbed bacterium *o*-17, that not only dechlorinates PCBs, but requires them in order to live (*Environ. Microbiol.* **3**, 699–709, 2001). Although aerobic microbes have been identified that can weaken chlorine bonds, thereby reducing the PCB to a less harmful state, bacterium *o*-17 breaks the chlorine bond in the critical *ortho* position, raising hopes that PCBs could, ultimately, be fully deactivated. *LF*