Notable advances 2011

Cardiovascular disease

A gut reaction

The way to a man's heart is through his stomach, the old adage goes. And new research suggests that the way to heart disease could be through the gut, too. Scientists from the Cleveland Clinic in Ohio and the University of California– Los Angeles screened small-molecule metabolites circulating in people's blood plasma and found that the presence of byproducts made after gut bacteria break down phospatidylcoline—a fatty substance found commonly in certain types of food—predicted who would later suffer from heart disease. Experiments in mice then showed that intestinal microbes have a central role in setting off a metabolic chain reaction that leads to this dietary lipid getting converted into a molecule called trimethylamine *N*-oxide (TMAO), whichboosts the formation of artery-clogging plaques that can lead to cardiovascular problems (*Nature* **472**, 57–63, 2011). These findings add to a growing body of evidence showing that commensal bacteria can cause or worsen certain conditions, including obesity and immune disorders. The work also suggests that drugs might be able to target TMAO to prevent atherosclerosis and heart disease. —*CP*

Infectious disease

Lost in transmission

Stopping HIV/AIDS requires a multifactorial approach, and a number of new strategies are proving effective at reducing infection rates. The latest success story came in July when members of the HIV Prevention Trials Network published a paper showing that initiating antiretroviral therapy soon after infection lowered the risk of HIV-positive individuals transmitting the virus to their uninfected sexual partners by 96% (*N. Engl. J. Med.* **365**, 493–505, 2011). The trial randomly assigned, 763 couples in which one partner was HIV positive to receive treatment either immediately upon enrollment or only when his or her CD4+ T cell counts declined to a previously specified point. After a median follow-up period of close to two years, 28 infections occurred that could be linked to the infected partner, but only one happened in the early-treatment group. The findings support administering antiretroviral therapy at earlier stages of the disease to slow the spread of HIV. —*AF*

Regenerative medicine

Direct conversion

Patient-specific stem cells derived by reprogramming adult cells to an embryoniclike state are ideal candidates for regenerative therapy because they can form any cell type in the body. But a major problem inherent to these so-called 'induced pluripotent stem cells' is that a subset of them may not mature into the cell type of choice following transplantation, and lingering stem cells can, unfortunately, trigger tumors. Now, two independent groups have figured out how to turn skin cells taken from people suffering from debilitating neurodegenerative diseases directly into functional neurons, thereby bypassing the need for a stem cell stage in between and, thus, possibly reducing the risk of cancer formation. In August, researchers from two institutions in New York achieved this feat in people with both spontaneous and familial forms of

Alzheimer's disease using a cocktail of five neural transcription factors (*Cell* **146**, 359– 371, 2011). A month earlier, an Italian team used just three transcription factors to convert skin cells from two women with genetic forms of Parkinson's disease into dopamineproducing neurons (*Nature* **476**, 224–227, 2011). —*EC*

Immunology

A helping hand

During an inflammatory reaction, the body often responds to low levels of oxygen by turning on a key transcription factor called hypoxia inducible factor-1□□(HIF-1□). This protein has long been known to help with cellular metabolism under naerobic conditions. But now, new evidence shows that HIF-1□□also influences the very immune cells driving the inflammatory response itself. Researchers from the Johns Hopkins University School of Medicine in Baltimore showed that HIF-1□□promotes the proliferation of T helper 17 (TH17) cells by activating ROR□t, a transcription factor crucial for TH17 differentiation. At the sametime, HIF-1□□also inhibits the development of regulatory T cells by mediating the degradation of another transcription factor called Foxp3 (*Cell* **146**, 772–784, 2011). The findings could have important therapeutic mplications. Ablating HIF-1□□in a mouse model of multiple sclerosis protected the animals from the development of TH17-
mediated disease, the researchers found, suggesting that targeting HIF-1□□could prove beneficial in a number of inflammatory contexts. —*KDS*

Gene therapy

In vivo improvement

In conference presentations this year, Sangamo BioSciences of Richmond, California announced clinical evidence showing that targeted genome editing technology can be used to make the human immune system resistant to HIV. This feat was achieved by modifying trial participants' T cells in the laboratory with designer enzymes called zincfinger nucleases. But, according to a preclinical study published in June, genome editing might be possible without having to remove cells from the body. In the first successful demonstration of this technology in living animals, researchers from the University of Pennsylvania Perelman School of Medicine in Philadelphia, in collaboration with Sangamo scientists, corrected the genetic defect in a mouse model of hemophilia. They injected mice with a virus encoding a zinc-finger nuclease together with
a virus modified to carry a normal version of the blood-clotting–associated gene *F9*. After treatment, the normal *F9* gene was present and correctly positioned in the genomic DNA of liver cells, and the animals' blood clotted faster with no signs of liver toxicity (*Nature* **475**, 217–221, 2011). —*MB*

Metabolism

Bile thumper

Bile acids are known to ward off fatty liver disease and maintain stable blood sugar levels. Thus, researchers have been on the lookout for ways to boost the production of these liver secretions. The liver receptor homolog-1 (LRH-1) protein is crucial for maintaining normal levels of bile acids, so a team led by scientists at the Baylor College of Medicine in Houston screened for small-molecule agonists of LRH-1. They found that a natural compound known as dilauroyl phosphatidylcholine (DLPC)—a trace component of lecithin, a common food ingredient derived from plant and animal sources—is a potent activator of both the mouse and human forms of the protein (*Nature* **474**, 506–510, 2011). In two different mouse models of obesity, the researchers showed that DLPC mildly increased bile acid levels in the blood, reduced fat generation by the liver and increased the rate at which the mice burned fat. These effects reduced the incidence of fatty liver disease and improved glucose tolerance and insulin sensitivity in the mice. The group's collaborators are now running a pilot clinical trial testing DLPC in prediabetic individuals.—*RL*