Notable advances 2013

From the microbiome to the microenvironment, certain areas of biomedicine saw fast-paced discovery this year. Here's a rundown of the papers that helped these fields advance quickly in 2013.

■ Stem cells

Live reprogramming

Ever since scientists first succeeded in creating induced pluripotent stem cells (iPSCs) from mouse cells in culture in 2006, efforts have focused on optimizing the process. This year, researchers at the Spanish National Cancer Research Centre (CNIO) in Madrid made a substantial advance in the field by creating iPSCs *in vivo* through the activation of key reprogramming factors in a living mouse (*Nature* **502**, 340–345, 2013).

In the new study, the iPSCs were derived *in vivo* from hematopoietic cells and organs of the gastrointestinal tract, pancreas and kidney. The significance of this work goes beyond the generation of a mouse with reprogrammable tissue; the iPSCs created *in vivo* reached a totipotent-like state and a plasticity that surpasses that of embryonic stem cells and other iPSCs made in a dish. Notably, these cells could differentiate into extraembryonic cells in culture and could form embryo-like structures consisting of the three germinal layers and tissues resembling the yolk sac. The *in vivo* reprogramming achieved this year may bring researchers one step closer to protocols that can accomplish controlled tissue reprogramming *in situ*. —*CP*

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■ Immunology

Innately important

In recent years, scientists have identified three main groups of innate lymphoid cells (ILCs), a family of immune cells that help fight infection and are a source of cytokines. The role such cells have in keeping the immune system in balance came into clearer focus this year when a team including researchers at the University of Pennsylvania's Perelman School of Medicine in Philadelphia found that mice lacking group 3 ILCs develop an exaggerated adaptive immune response to commensal bacteria that normally live in the mouse gut (*Nature* **498**, 113–117, 2013). Using genetic- and antibody-mediated depletion of ILCs, they demonstrated that ILCs can reign in the immune response of $CD4^+$ T cells to commensal bacteria and maintain immune homeostasis in the gut.

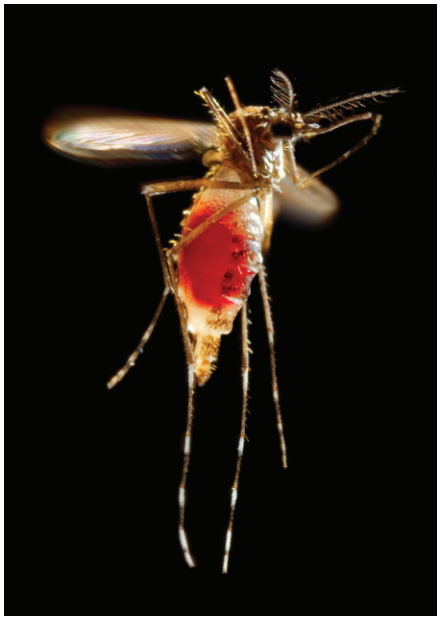
Meanwhile, scientists from the University of California–San Francisco found that type 2 ILCs continuously produce interleukin-5 (IL-5), helping regulate numbers of infection-fighting eosinophils. In response to helminth infection or caloric intake, these cells co-express IL-5 and IL-13, promoting the accumulation of eosinophils in tissues (*Nature* **502**, 245–248, 2013). Given ILCs' sentinel role in tuning immune responses, drugs that target them may one day be developed to treat inflammatory disease. —*KDS*

■ Infectious disease

In a different vein

About four decades ago, scientists demonstrated that a person exposed to more than a thousand bites from mosquitoes carrying a radiation-attenuated version of a *Plasmodium* parasite would develop immunity against malaria. But translating this strategy of insect exposure to the clinic is impossible. An attempt to mimic this method with cryopreserved versions of attenuated *Plasmodium falciparum* sporozoites delivered through intradermal or subcutaneous vaccination showed in 2011 that this approach was safe in humans—but did not protect against infection.

A different method of delivery might work: researchers at the US National Institutes of Health's Vaccine Research Center in Bethesda, Maryland, and their collaborators have shown that intravenous delivery of the sporozoite-based vaccine successfully protected human volunteers against infection in a dose-dependent manner; none of the six volunteers who received the highest vaccine dosage became infected, whereas five of the six participants in the control group did (*Science* **341**, 1359–1365, 2013). The findings come at a promising time for the field, with follow-up phase 3 data showing that the RTS,S vaccine cut malaria cases by 46% among youngsters aged 5 months to 17 months. —*AF*



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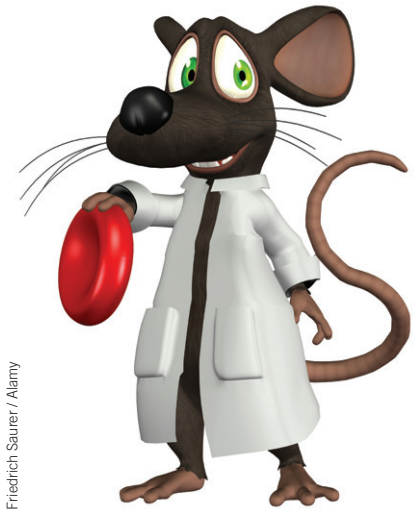
■ Cardiovascular disease

Young at heart

The blood of a young mouse can rejuvenate an old mouse when researchers surgically connect the circulatory systems of the two. Using this experimental setup, a team that included researchers from the Brigham and Women's Hospital in Boston has now identified a cytokine, growth differentiation factor 11 (GDF11), as a factor in young mouse blood that can reverse age-related heart remodeling (*Cell* **153**, 828–839, 2013).

Enlargement of the heart occurs with aging and is thought to contribute to diastolic heart failure, a common form of heart disease in the elderly. This type of cardiac enlargement also occurs in aged mice. But when the scientists connected the circulatory systems of young mice to that of aged mice, the enlarged hearts

of the older rodents shrank after four weeks. To identify the heart-shrinking molecule in the blood, they screened for blood proteins whose levels decline with age. One of these, GDF11, could reduce the size of cardiac muscle cells cultured *in vitro*, and injection of aged mice with GDF11 alone had the same rejuvenating effect on the heart as exposure to young blood. GDF11 treatment might therefore be used to rehabilitate the aging heart. —*MB*



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■ Neuroscience

The painful truth

Contrary to what pain researchers previously thought, inflammatory molecules and immune cells might not necessarily be responsible for the pain experienced during bacterial infections. Instead, the bacteria themselves directly activate pain neurons, according to findings led by a group at Boston Children's Hospital (*Nature* **501**, 52–57, 2013).

The researchers infected the paws of mice using a community-associated strain of methicillin-resistant *Staphylococcus aureus* (MRSA) bacteria and found that the waxing and waning of pain in the mice correlated with bacterial load, not with local swelling or the levels of proinflammatory cytokines. They observed similar pain patterns in mice lacking various types of immune cells. Crucially, formyl peptides released from MRSA seemed to activate formyl peptide receptors on sensory neurons in culture, and mice lacking these receptors had reduced pain when infected with the superbug. In addition, a pore-forming toxin released by MRSA called α-hemolysin caused the excitement of sensory neurons in culture and induced pain when injected into mice, presumably by poking holes in the membranes of the neurons and allowing ions to flow through. The findings could provide new therapeutic targets to fight pain during infections. —*EC*

■ Animal models

A CRISPR edge

This year marked the rise of a genome-editing technique that combines target sequences with components from a bacterial immune system called CRISPRs (clustered regularly interspaced short palindromic repeats), which direct an enzyme, Cas, to edit out specific DNA stretches. Scientists from the Broad Institute in Cambridge, Massachusetts, used CRISPR technology to edit several genomic sites in mammalian cells at once (*Science* **339**, 819–823, 2013) and researchers at Harvard Medical School (HMS) in Boston created a library of 190,000 RNA CRISPR guide sequences that collectively target 40% of human exons (*Science* **339**, 823–826, 2013).

CRISPR editing may make it faster to create animal models of disease. For example, another team from HMS used the technique to engineer mutations in ten genes in zebrafish embryos (*Nat. Biotechnol.* **31**, 227–229, 2013). Meanwhile, researchers from the Whitehead Institute in Cambridge, Massachusetts, used a single-step CRISPR method to generate mice with mutations of two different genes (*Cell* **153**, 910–918, 2013); they later used it to create mice in which the targeted gene could be switched off at a certain stage or in a certain cell type (*Cell* **154**, 1370–1379). —*MS*

■ Cancer

Motley malignancies

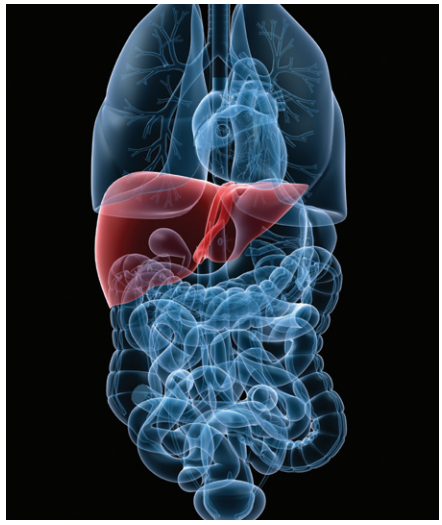
This year saw considerable advances in scientists' understanding of how the intrinsic variation seen in the genetic makeup and cellular landscape of tumors influences the growth of these malignancies—as well as their resistance to therapy. A study from the Dana-Farber Cancer Institute in Boston, for example, analyzed cancer samples taken from 149 people with chronic lymphocytic leukemia and detailed distinct mutations that appeared to drive the growth of cancer cell subpopulations, and it linked these mutations to disease outcomes (*Cell* **152**, 714–726, 2013). Additionally, researchers at the Ontario Cancer Institute in Toronto and their collaborators tracked subpopulations of colorectal tumor cells and showed how chemotherapy can exert selective pressure leading to the dominance of previously minor subpopulations (*Science* **339**, 543–548, 2013).

Meanwhile, a paper on prostate cancer offered the new term 'chromoplexy' to describe the genomic rearrangements that may drive the punctuated evolution of tumors (*Cell* **153**, 666–677, 2013). These and other studies suggest that tumor heterogeneity is an underappreciated phenomenon worthy of further exploration to understand how cancers evolve. —*VA*

■ Metabolism

Beta testing a new hormone

As insulin resistance rises in the liver, the body appears to compensate with an increase in the volume of insulin-producing beta cells in the pancreas. Scientists have long sought to pinpoint which circulating signaling molecules might cause this cell growth. This year, researchers at Harvard University in Cambridge, Massachusetts, identified one such hormone, which they dubbed betatrophin (*Cell* **153**, 747–758, 2013).



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The investigators found that mice with drug-induced diabetes—as well as obese mice—display a large increase in betatrophin in the liver and white fat tissue, but not in beta cells. They then showed that boosting betatrophin levels in the liver prompted beta cells to grow and divide while also improving glucose tolerance. Despite the excitement elicited by this study, the jury on betatrophin is still out: scientists at the University of Texas Southwestern Medical Center in Dallas deleted the gene encoding this hormone in mice and saw no changes in glucose metabolism—including in those fed a high-fat diet—although they did not examine cell changes in the pancreas (*Proc. Natl. Acad. Sci. USA* **110**, 16109–16114, 2013).—*RL*

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