

Notable advances

Some of the key papers published in 2009

■ Lifespan

When rapamycin was fed to older adult mice in a July study, the immunosuppressive drug increased average lifespan by 9% in males and 14% in females, for as yet unknown reasons (*Nature* 460, 392–395; 2009). A 20-year longitudinal study on rhesus monkeys also lent more support to the benefits of caloric restriction: cutting calories by 30% slashed the monkeys' cancer and cardiovascular disease rates in half, protected them from diabetes and increased their lifespan (*Science* 325, 201–204; 2009).

■ T-cell Immunity

Vaccinologists may find new promise in immunosuppressive drugs and antidiabetes medications. In June, researchers discovered that rapamycin, a drug typically administered to transplant patients, boosts the magnitude and quality of the CD8⁺ memory T cell response in mice challenged with a virus (*Nature* 460, 108–112; 2009). And, in the same month, another team reported that healthy mice given the antidiabetes drug metformin in conjunction with an experimental vaccine were more likely to survive a tumor challenge than those given the vaccine alone. When fatty acid metabolism is optimized, effector T cells may more easily develop into memory T cells (*Nature* 460, 103–107; 2009).

■ Hepatitis C

Why do some patients with hepatitis C respond to treatment better than others? This year, three genome-wide association studies on a total of more than 2,000 individuals identified a single nucleotide polymorphism on chromosome 19 that may play a big part in treatment response. The genotype favoring better viral clearance is more prevalent in European populations than African populations and explains half the response rate difference between patients with these two ancestries (*Nature* 461, 399–401; 2009; *Nat. Genet.* 41, 1100–1104; 2009; *Nat. Genet.* 41, 1105–1109; 2009). Further analysis by an independent group of researchers revealed that the genetic variations, which lie upstream of the gene encoding type III interferon IFN- λ 3, also strongly influence whether individuals can naturally clear HCV infection (*Nature* 461, 798–801; 2009).

■ HIV

The results of a multicenter placebo-controlled trial conducted in Thailand brought good news for the HIV field. A recombinant canarypox vaccine expressing a handful of HIV-1 proteins, given in combination with a recombinant glycoprotein 120 subunit vaccine, was about 30% effective at preventing HIV-1 infection in 16,395 mainly heterosexual men and women over the course of three years (*N. Engl. J. Med.* doi:10.1056/nejmoa0908492; 2009).

■ microRNA

Many cancer therapies are being designed to inhibit oncogenic miRNAs, but a more promising goal might be to replace some of the many miRNAs that go missing. When researchers restored expression of an miRNA in cancer cells that is normally expressed in healthy liver cells, cancer growth slowed, and tumor cells died without adverse effects (*Cell* 137, 1005–1017; 2009).

■ Prions and Alzheimer's Disease

Yale researchers discovered a potentially important link between the brain's normal noninfectious prion proteins and the amyloid- β peptides that are the hallmark of Alzheimer's disease. When they prevented prions and amyloid proteins from binding one another in mouse brain tissue, electrical signaling between cells improved, suggesting that interaction between the two contributes to disease development (*Nature* 457, 1128–1132; 2009).

■ Bone

The hormone leptin regulates not just appetite and energy expenditure but also bone mass, and a longstanding question has been whether it works alone or in concert with other compounds. Researchers identified brain-derived serotonin as one of leptin's key targets: leptin inhibits serotonin formation in the brainstem, preventing it from doing its job in the hypothalamus, such as increasing bone mass and appetite and reducing energy use. The results expand the known roles of brain-derived serotonin and identify a molecular basis for the common central control of bone mass and appetite (*Cell* 138, 976–989; 2009).

■ Tuberculosis

New hope is on the horizon in the fight against drug-resistant tuberculosis. Antibiotics such as meropenem have always been ineffective against *Mycobacterium tuberculosis* because a bacterial protein degrades the drug, but researchers showed this year that when the β -lactamase inhibitor clavulanate is administered along with meropenem, drug-resistant *mycobacteria* die (*Science* 323, 1215–1218; 2009).

A major way in which *M. tuberculosis* subverts host cell signaling is by manipulating the second messenger cyclic AMP in host cells. A study pushed in July suggests that compounds that inhibit specific adenylate cyclase genes could help fight infection (*Nature* 460, 98–102; 2009). Other researchers identified a compound called oxazolidin-2—one that prevents essential protein degradation in nonreplicating *M. tuberculosis* without adversely affecting human cells (*Nature* 461, 621–626; 2009). And, in May, researchers reported the synthesis of a new benzothiazinone called BTZ043 that kills *M. tuberculosis* by blocking formation of arabinan, an important component of the bacterial cell wall (*Science* 324, 801–804; 2009).

■ Cardiology

Researchers took advantage of a Cold War artifact to show that human heart cells renew themselves. In the 1950s, nuclear weapons tests filled the atmosphere with radioactive carbon-14, an isotope that then made its way into human cells as they regenerated—providing a kind of cellular time stamp. Researchers analyzed heart cells for this isotope and concluded that roughly half of all cells in a typical 50-year-old's heart are generated after birth. By developing ways to stimulate this endogenous regenerative process, scientists could heal damaged hearts without having to introduce stem cells or other cell progenitors (*Science* 324, 98–102; 2009).

■ RNA Interference

Boston researchers overcame a major challenge in RNAi-based medicine—safely getting the therapy to the right tissues—by developing an oral RNAi-based therapeutic that quiets inflammation in mice. The therapy silences the expression of a cytokine mediator called Map4k4 that has a role in autoimmune diseases including rheumatoid arthritis, Crohn's disease and atherosclerosis (*Nature* 458, 1180–1184; 2009).

Melinda Wenner, New York