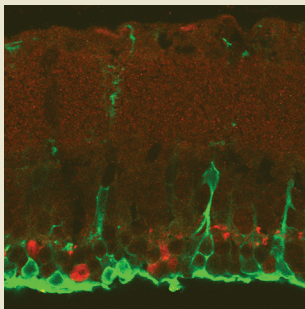


Retinal rejuvenation

Blindness caused by the loss of cone or rod photoreceptor cells in the retina may be amenable to cell-replacement therapy. Building on a previous paper showing a functional benefit from grafting of postmitotic rod photoreceptors, Reh and colleagues studied transplantation of retinal cells differentiated from human embryonic stem cells, a cell type that can be expanded without limit. Two to three weeks after injection of 50,000–80,000 retinal cells into the subretinal space of wild-type adult mice, some of the cells had migrated to the outer nuclear layer (the normal location of photoreceptors), adopted photoreceptor morphology and expressed the photoreceptor markers rhodopsin and recoverin. When the same protocol was applied to adult *Crx*^{-/-} mice, which are incapable of any photoreceptor electroretinographic response, 15 of 23 animals acquired the ability to respond to flashes of light. These results establish that human embryonic stem cells differentiated to retinal cells *in vitro* can restore some degree of visual function *in vivo*. (*Cell Stem Cell* 4, 73–79, 2009)



KA

Vaccines and antibody maturation

Vaccine development is often hampered by a weak and low-avidity antibody response, leading to, at best, incomplete protection and, at worst, greater severity of the infection. Working on respiratory syncytial virus (RSV), a leading cause of infant hospitalization, Delgado *et al.* identify maturation of antibody affinity as a key factor for safe and efficient immunization. They compare the immune response to nonreplicating vaccines, including a failed vaccine from the 1960s that caused an enhanced respiratory disease, with the response to wild-type virus in mice. Whereas mice challenged with wild-type RSV produce a repertoire of antibodies with increasingly high affinity over time, no affinity maturation is observed with nonreplicating vaccines. The authors identify the activation of Toll-like-receptors (TLRs) as the main determinant for antibody maturation. When combined with a cocktail of specific activators of different TLRs, nonreplicating vaccines show affinity maturation similar to wild type virus and protect mice from enhanced respiratory disease. This underscores the importance of TLR activation in developing better adjuvants and enhancing immunization strategies. (*Nat. Med.* 15, 34–41, 2009)

ME

Keeping sepsis at bay

Sepsis kills as many people annually as heart attacks, yet current therapies often fail to stop fatal progression to organ failure. Now Németh and colleagues report that, in a mouse model of sepsis, the infusion of bone marrow stromal cells (BMSCs) does just that. Injecting a million BMSCs around the time that sepsis was induced (by ligating and then puncturing the cecum) led to a 50% reduction in death and spared liver, kidney and spleen. In mice receiving transplants, serum

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concentrations of inflammatory cytokines (tumor necrosis factor- α and interleukin (IL)-6) rose only slightly, whereas concentrations of the anti-inflammatory IL-10 were elevated. A fluorescent dye allowed the path of transplanted cells to be followed from the blood through the lungs (and spleen and liver). The transplanted cells were surrounded by macrophages in the lung, which led the researchers to ask what role such cells might play in the outcome. In a combination of *in vivo* and *in vitro* experiments using mice deficient in various cytokines, the researchers show that the BMSCs, after binding bacterial lipopolysaccharide, reprogram macrophages into releasing IL-10, which in turn prevents the infiltration of neutrophils into organs, a source of organ damage and pathogenesis. Autologous and allogeneic BMSCs worked equally well, which bodes well for a potential human therapeutic. (*Nat. Med.* 15, 42–49, 2009)

LD

Bacteria shorten mosquito life

Unlike fine wine, pathogen-carrying mosquitoes do not improve with age. Pathogens such as those that cause dengue fever and malaria must mature in their mosquito hosts for about 2 weeks before they are able to cause disease. McMeniman *et al.* devise an ingenious way of controlling pathogen transmission, taking advantage of this incubation period by developing a strain of bacteria that shortens the lifespan of *Aedes aegypti*, the dengue vector. By serially passaging a strain of the bacterial symbiont *Wolbachia* in mosquito cell culture for 3 years, the researchers weaned the bacterium from its natural host so that it can target *A. aegypti*. In laboratory trials, the lifespan of *Wolbachia*-infected mosquitoes is halved—a reduction predicted to be sufficient to reduce pathogen transmission and the incidence of human disease. The microbial control agent should spread rapidly through natural populations because infected female mosquitoes pass the bacteria to their offspring and cytoplasmic incompatibility prevents uninfected females from reproducing with infected males. And because the bacteria kill mosquitoes long after they have reached sexual maturity, the approach should not compromise reproductive fitness. It may thus be less prone to the emergence of insect resistance, which is problematic with alternatives such as insecticide application. (*Science* 323, 141–144, 2009)

CM

Fc γ RIIa inhibitors get in the groove

Encouraged by evidence that inhibition of the primate-specific Fc γ receptor IIa (Fc γ RIIa) may provide new therapies for autoimmune diseases such as rheumatoid arthritis and lupus erythematosus, Pietersz *et al.* exploit knowledge of the three-dimensional structure of the Fc γ RIIa ligand-binding site to design >100 small-molecule inhibitors predicted to target the groove formed by receptor dimerization. They assess these *in vitro* by screens for inhibition of platelet activation and aggregation, as well as capacity to inhibit tumor necrosis factor- α secretion from macrophages, and test *in vivo* the five most promising candidates using a collagen-induced arthritis (CIA) model involving transgenic mice expressing human Fc γ RIIa. The strongest inhibitor not only shows better long-term suppression of CIA than methotrexate, immunosuppressive anti-CD3 antibody or Fc γ RIIa-specific antibody fragments, but also does not inhibit CIA in a CIA-susceptible mouse not expressing Fc γ RIIa. Although none of the compounds are able to control established disease, their ability to antagonize Fc γ RIIa activity downstream of immune-complex formation could make them promising leads in the pursuit of less immunosuppressive anti-inflammatories for certain autoimmune diseases. (*Immunol. Cell Biol.* 87, 3–12, 2009)

PH