

### In This Issue

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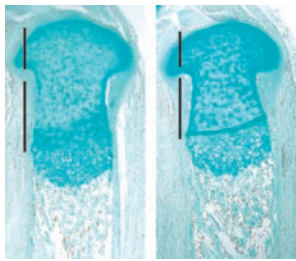
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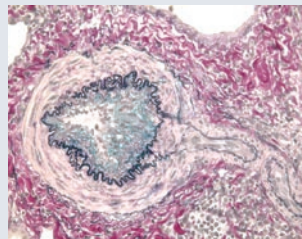
### Ihh can hone the bone

Normal growth and development of the bones rely on coordination between chondrocyte mass regulation and cartilage structure establishment. Parathyroid hormone-related protein (PTHrP) and Indian hedgehog (Ihh) are important for the precise regulation of cartilage development, but the mechanisms that guide chondrocytes through the growth plate during bone formation were not well understood. In this issue, Kobayashi et al. (pages 1734–1742) examine the control of early chondrocyte differentiation by Ihh and the physiological role of this differentiation step in regulating chondrocyte mass and growth plate composition. The researchers analyze mice carrying multiple genetic modifications, in which expression of PTHrP, PTHrP receptor, and Ihh or combinations of these molecules were modified. Their analysis

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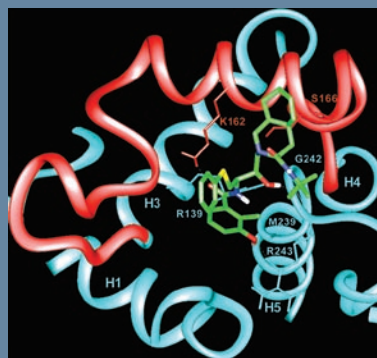
### Learning lessons in lupus

T cells are hyperactive, aberrant, or both in human and murine lupus. *Sle3* is a lupus susceptibility locus on murine chromosome 7 that is associated with spontaneous T cell hyperactivity and auto-reactivity when placed into B6 mice with normal genetic backgrounds. In this issue of the *JCI*, Zhu et al. analyze the means by which *Sle3* affects the phenotype of the B6.*Sle3* congenics in which there is T cell hyperactivity as well as elevated CD4/CD8 ratios and levels of anti-nuclear antibodies (pages 1869–1878). The researchers demonstrate that these B6.*Sle3* congenic mice exhibit heightened T cell expansion *in vitro* upon antigen challenge, mediated by hyperstimulated antigen-presenting cells. The DCs and macrophages derived from congenics are more mature/activated and induce superior costimulation to T cells *in vitro* compared with those from controls. Finally, adoptive transfer of B6.*Sle3*-derived DCs into B6 mice increases the CD4/CD8 ratio and the level of serum anti-nuclear antibodies. That *Sle3* causes aberrant activation of antigen-presenting cells is a novel observation, and this trigger might account for the hyperactivity of T cells and breach in self tolerance seen in lupus. This new information has important implications for our understanding of autoimmune disease and how to manage it clinically.



### Monkeying around to improve organ transplantation

Organ transplantation is accompanied by nonspecific immune suppression therapy to prevent T cell-mediated rejection. The immunosuppressants used can cause infection, hypertension, cancer, and other undesirable side effects. Therefore, specific suppression of alloreactive T cells is needed. It was known that anergic T cells generated *ex vivo* have immunosuppressive activity *in vitro*, and now Bashuda et al. investigate whether this approach can induce indefinite organ allograft survival in 6 rhesus monkeys (pages 1896–1902). The authors stimulate recipient T cells from nonhuman primates with donor cells under conditions associated with the development of T cell anergy. Reinfusion of these cells into the recipient after kidney transplantation leads to very prolonged — 880 days — and perhaps even indefinite graft survival in 3 long-surviving animals without administration of additional immunosuppressive agents. The cell inoculum is anergic *in vitro*, mediates *in vitro* suppressor activity, and has a CD4<sup>+</sup>CD25<sup>+</sup> phenotype. This study shows for the first time that anergic T cells generated *ex vivo* suppress renal allograft rejection in nonhuman primates. This may be an approach that could be used in human transplant trials.



### Protease inhibitors reach beyond HIV

The immunodeficiency that arises in HIV may be due to excessive apoptosis of CD4 T cells. HIV protease inhibitors (PIs) can block apoptosis in virus-infected T cells *in vitro* but have also been shown to induce apoptosis at higher concentrations. The mechanisms underlying these paradoxical data are unclear, as is whether PI therapy would aid CD4 T cell reconstitution in HIV patients *in vivo*. Now Weaver et al. (pages 1828–1838) examine whether PIs are antiapoptotic *in vivo* and the mechanisms involved. The authors show that HIV PIs block apoptosis induced by 3 relevant, virus-independent mouse models — mice with Fas-induced hepatitis, *Staphylococcal*-induced shock, and experimental stroke. In each model, HIV PIs block apoptosis and improve histology, survival, and function. The PIs prevent apoptosis by directly inhibiting mitochondrial permeability transition to prevent pore formation and maintain mitochondrial integrity. These data show that PIs are antiapoptotic *in vivo* and that related compounds may be useful in the treatment of non-HIV disorders also characterized by excess apoptosis.