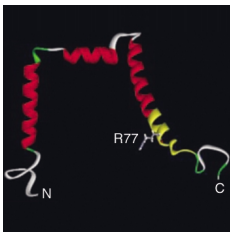
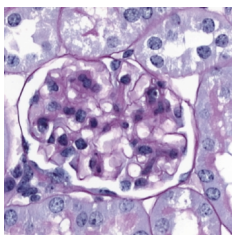
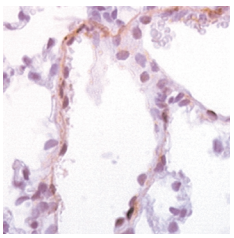


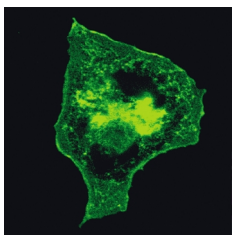
Preventing progression of HIV. A subset of HIV-infected patients do not progress to AIDS, despite persistently high levels of viral replication. Since these "nonprogressors" are known to have lowered levels of apoptosis, Andrew Badley and colleagues (pages 1547–1554) investigated abnormalities in their apoptosis induction and regulation. The authors discovered a polymorphism present within the apoptosis-inducing domain of viral protein R (Vpr) that occurs at high frequency in nonprogressors. This is in contrast to the relatively rare frequency of this mutation in most patients with progressive HIV disease. The authors also show that infection with HIV-1 in patients with normal Vpr was associated with more apoptosis than HIV-I infection in those carrying the polymorphism in Vpr. This study suggests that Vpr activity can contribute to viral pathogenicity and may lead to a new therapeutic target for HIV patients.



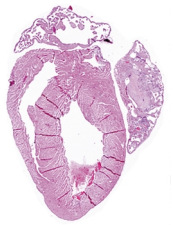
Throwing lupus for a loop with CD137. Systemic lupus erythematosus (SLE) is a $CD4^+$ T cell–dependent autoimmune disease that primarily affects women of childbearing age. Treatment of SLE often relies on glucocorticosteroids, which leave patients susceptible to infections, cytotoxicity, diabetes, bladder cancer, and hypertension. Robert S. Mittler and colleagues have now discovered that treatment of SLE-prone mice with antibodies to the T cell costimulatory receptor CD137 can reverse established disease and extend survival without the side effects seen with steroid treatment (pages 1505–1518). Anti-CD137 antibodies were used to suppress $CD4^+$ T cells and hence decrease the levels of $CD4^+$ T cell–derived pathogenic autoantibodies. Early data from the authors in nonhuman primates has shown that this treatment strategy could potentially be extended to humans suffering from lupus.



A new therapy for pulmonary hypertension? Pulmonary hypertension is a common complication of chronic obstructive pulmonary disease, often leading to right ventricular hypertrophy and heart failure. Current treatment with oxygen, bronchodilators, and vasodilators has had limited success and merely delays progression of the disease, often necessitating lung transplantation. In the present study, Peter Carmeliet and colleagues provide genetic, functional, and morphological evidence for an important role of hypoxia inducible factor–2α (HIF-2α) in the pathogenesis of pulmonary hypertension (pages 1519–1527). In addition, the authors provide mechanistic insight into the role of some of the HIF-2α targets (endothelin, eNOS, catecholamines) responsible for the development of pulmonary vascular remodeling. These results raise the possibility that inhibition of HIF-2α may have a therapeutic role in the treatment of pulmonary hypertension.



Arrhythmia unraveled. Sinus node dysfunction (SND) accounts for approximately half of all patients requiring implanted pacemakers. In a significant portion of patients with SND, there are no obvious identifiable cardiac abnormalities or other associated conditions, and the disease's etiology remains unclear. In their study of an SND patient (pages 1537–1545), Eric Schulze-Bahr and colleagues show that SND can be caused by a previously unidentified mutation in the cardiac pacemaker ion channel gene *HCN4* that is thought to be one of the major determinants of sinus node rhythmicity. This mutation in the HCN4 channel leads to production of a C-terminal truncated protein that lacks a cyclic nucleotide-binding domain. The authors propose that the sinus bradycardia in the patient is caused by the truncated HCN4 subunit. This finding represents the first example of a human genetic mutation in the HCN family of pacemaker channels.



At the heart of hypertrophy. Cardiac hypertrophy is thought to benefit the heart by maintaining pump function during heart failure, but prolongation of hypertrophy can lead to arrhythmia and sudden death. The MAPK signaling cascade is an attractive intermediate target for pharmacologic intervention in treating hypertrophy, given its characteristic activation in response to most hypertrophy-associated stimuli. Since the role of the p38-MAPK pathway in the heart has been controversial, Jeffrey Molkentin and colleagues used a cardiac-specific transgenic mouse model to show that genetic inhibition of p38α signaling predisposes the heart to greater postdifferentiated growth (page 1475–1486). The authors further demonstrate the mechanism of p38-MAPK involvement by showing that p38α signaling antagonizes the growth of postmitotic cells by directly blocking calcium-induced growth effects through calcineurin-NFAT.