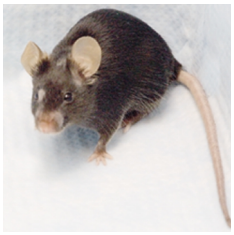
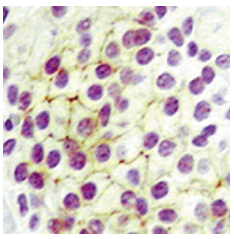
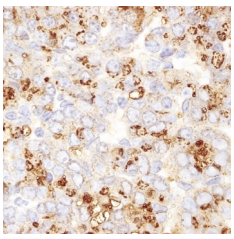


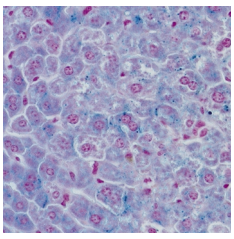
PDE4, emesis, and non-vomiting mice. Inhibition of phosphodiesterase 4 (PDE4) attenuates inflammatory responses in the airways, but the therapeutic potential of PDE4 inhibitors has been limited by side effects such as nausea and emesis. PDE4 inhibitors are thought to have similar effects to inhibitors of α_2-adrenoceptor in neurons and thereby thought to affect the emetic reflex. In an effort to identify PDE4 inhibitors that lack these side effects, Annette Robichaud and colleagues have turned to the mouse. One complication is that mice — like all rodents — don't vomit. As a substitute, the researchers examined the different PDE4 subtypes for their roles in reversing α_2-adrenocpetor–mediated anesthesia. Their results (pages 1045–1052) suggest that PDE4D, but not PDE4B, is the major mediator of emesis induced by PDE4 inhibitors. The contributions of PDE4A and PDE4C require further clarification.



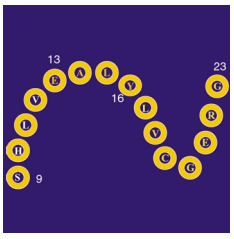
Controlling insulin secretion. Early in the development of type 2 diabetes, pancreatic β cells proliferate to compensate for their deteriorating ability to synthesize, store, and secrete insulin in response to metabolic changes. Several lines of evidence have implicated the type 1 IGF receptor (IGF1R) in β cell proliferation, but the perinatal lethality associated with lack of IGF1R function in knockout mice has precluded the in vivo analysis of IGF signaling through this receptor in β cells. Argiris Efstratiadis and colleagues have engineered mice that specifically lack IGF1R in β cells. Unexpectedly, these mice had normal β cell mass but revealed a hitherto unrecognized role for IGF1R-mediated signaling in insulin secretion (see pages 1011–1019).



Pituitary proliferation. Growth of lactotrophs — prolactin-producing cells in the pituitary — is controlled through a negative feedback loop that involves the action of prolactin on dopaminergic neurons in the hypothalamus. Subsequent neuronal dopamine release and binding to lactotroph D2 receptors inhibits lactotroph proliferation. To investigate whether prolactin also affects lactotrophs directly, Malcolm J. Low and colleagues compared mice lacking D2 receptors with prolactin receptor knockout mice (pages 973–981). Females from both mutant strains developed large prolactinomas — pituitary adenomas that produce prolactin. Males had smaller tumors overall, but a significant difference between the two strains emerged: Males lacking the prolactin receptor had larger tumors and higher prolactin levels, along with an additive effect of the compound mutations. Together with data from pharmacologic studies, these results suggest that prolactin inhibits lactotrophs through two distinct mechanisms, indirectly through dopaminergic neurons in the hypothalamus, and directly through an autocrine or paracrine loop in the pituitary.



Hepcidin and iron regulation. Iron homeostasis is critical for human health. As mammals cannot regulate iron excretion, homeostasis depends on the regulation of dietary iron absorption in the duodenum in response to metabolic needs. Previous studies by Sophie Vaulont and colleagues had implicated hepcidin, a small peptide synthesized in the liver, in the regulation of iron uptake. Usf2 knockout mice lack hepcidin and develop iron overload, whereas overexpression of a hepcidin transgene in the liver leads to iron deficiency and anemia. A study in this issue (pages 1037–1044) that examines hepcidin levels in other conditions further supports a central role for the peptide in iron homeostasis. Hepcidin mRNA levels dramatically decreased in anemia and hypoxia (both conditions of increased iron absorption), and increased several-fold in response to inflammation. In wild-type mice, this increase was associated with a two-fold decrease in serum iron, whereas iron levels stayed constant, despite inflammation, in mice that lacked hepcidin.



Anaphylaxis in response to insulin vaccination in NOD mice. More than 90% of insulin-reactive T cells from islets of NOD mice react with a particular part of the insulin protein, known as peptide B:9-23. Its sequence is identical in mouse and man, and human T cells also recognize the peptide. Vaccination with an altered peptide ligand of B:9-23 can suppress diabetes in the NOD mouse model, and it is currently in phase 1 clinical trials. Having been involved in mouse studies that used the peptide in the presence of Freud's adjuvant, George S. Eisenbarth and colleagues have continued to investigate different vaccination regimes in NOD mice. As they report beginning on page 1021, administration of the peptide in the absence of adjuvant provoked a fatal anaphylactic response in NOD mice that depended on the age at vaccination onset, the mode of administration, and the dose. This is an initial report that leaves many questions open, and its relevance for the human situation is unclear. Nevertheless, clinicians involved in studies of peptide vaccines should be aware of the results.