Primate model for Huntington's

Yang *et al.* report a transgenic rhesus macaque model of Huntington's disease (HD) that may improve insight into the pathology of this heritable neurodegenerative disease and reveal potential therapies. Following lentiviral delivery of the mutated human huntingtin (*HTT*) gene and green fluorescent protein into mature rhesus oocytes and transfer of the transgenic embryos to surrogate mothers, five pregnancies were carried to full term. Three of the newborns, which died within a month, carried multiple copies of mutated *HTT* and displayed severe behavioral symptoms and neuropathological features that are hallmarks of HD. Of the other two—twin males carrying single copies of mutated *HTT*—one showed no disease symptoms after six months, whereas the other displayed motor dysfunction similar to that seen in HD patients. It is hoped that disease progression in these two monkeys can be monitored and that they can be used to establish lines with consistent phenotypes that mimic human behavioral, cognitive and neuroanatomical features better than rodent models of HD. (*Nature* **453**, 921–924, 2008) *PH*

Bortezomib attenuates lupus-like disease

Glucosteroid- and cyclophosphamide-based immunosuppressive therapies show poor efficacy in the treatment of autoantibody-mediated disorders like systemic lupus erythematosus (SLE). Neubert *et al.* show that the clinically approved proteasome inhibitor bortezomib depletes plasma cells producing antibodies against DNA, reduces inflammation in the kidney and extends survival in two different lupus-like mouse models— NZB/W F1 and MRL/lpr mice. Whereas dexamethasone and cyclophosphamide only reduce the number of short-lived plasma cells after 7 days of treating NZB/W F1 mice, bortezomib efficiently depletes both short-lived and long-lived plasma cells, thereby effectively reducing autoantibodies against DNA. Bortezomib most likely depletes both plasma cell populations by activating the terminal unfolded protein response, as the mRNA levels of the chaperone BiP and the proapoptotic factor Chop are substantially increased in splenic B cells. They further show that bortezomib not only prevents lupus-like disease in NZB/W F1 mice but, more importantly, also has a substantial therapeutic effect in more advanced disease in NZB/W F1 and MRL/lpr mice. Clinical studies are required to determine whether proteasome inhibitors are effective in treating human SLE disease. (*Nat. Med.* **14**, 748-755, 2008) *JWT*

Safer radiotherapy?

A mechanism underlying the gastrointestinal damage caused by radiation of the abdomen has been identified, suggesting a new approach to mitigating the toxicity of cancer radiotherapy. A protein called p53 upregulated modulator of apoptosis (PUMA) is known to mediate apoptosis, and repression of PUMA has been found to prevent apoptosis induced by p53, DNA damage and hypoxia in a range of cell types. Qiu *et al.* report that PUMA is also involved in the death of intestinal stem and progenitor cells after radiation, a process that can lead to 'gastrointestinal syndrome' and limits the use of abdominal and pelvic radiotherapy. Whole-body radiation of mice upregulated *PUMA* gene expression several fold and induced apoptosis in intestinal lower crypt cells. In contrast, irradiated *PUMA* knockout mice fared better, showing increased resistance to apoptosis, enhanced crypt regeneration and improved survival. Moreover, radiation-induced intestinal damage of wild-type mice could be alleviated by treatment with antisense oligonucleotides targeting *PUMA*. (*Cell Stem Cell* **2**, 576–583, 2008) *KA*

Written by Peter Hare, Jan-Willem Theunissen, Kathy Ascheim & Laura DeFrancesco

Metastasis instigator revealed

Tumor metastases cause more cancer deaths than primary tumors, yet no therapy exists that targets metastatic tumors. Work by McAllister and colleagues now points to osteopontin, a cytokine produced by tumor cells, as one element that controls this process. The researchers developed a protocol in a rodent model to probe the influence of primary tumors on distant sites—bilateral xenograft implantation. Using this system, they find that only certain tumor cells, among them transformed human mammary epithelial cells (termed instigator cells), when injected subcutaneously into the flanks of mice, can influence the growth of tumor xenografts (responding cells) in the opposite flank. They show that the effect involves bone marrow–derived hematopoietic stem cells, which are enriched in the distant tumors when compared with the control (rodents implanted with Matrigel alone or with noninstigating tumor cells). In animals with instigating xenografts, quiescent progenitor cells are depleted from the bone marrow. Finally, in a screen of over 80 serum proteins, they identify only one (osteopontin) that can mimic the effects of instigator cells in their model. Osteopontin, which has been previously shown to be elevated in people with metastatic disease, may provide a new target for intervention in this deadly form of cancer. (*Cell* **133**, 994–1005, 2008) *LD*

Putative plasma biomarkers for pancreatic cancer

Noninvasive, presymptomatic diagnosis will be key to improving the prognosis for pancreatic adenocarcinoma, which has a five-year survival rate of only 3%. To address this need, Faca *et al.* analyze plasmas from a well-characterized transgenic mouse model that recapitulates the pathogenesis of human pancreatic cancer. A protein fractionation strategy that permits identification of proteins spanning abundances differing by seven orders of magnitude enables them to identify 45 proteins found at higher levels in cancer samples than controls and thought to be relevant to pancreatic cancer. Of these, nine are assayed in sera from patients diagnosed with early-stage pancreatic adenocarcinoma, matched healthy individuals and patients with chronic pancreatitis (a noncancerous, inflammatory condition that might complicate diagnosis). The effectiveness of five of these proteins to discriminate cancer samples from matched controls is demonstrated in a blinded analysis of sera from 26 humans, 13 of whom were diagnosed with pancreatic cancer 7–13 months after blood draw. Although independent studies have previously implicated some of the five markers in cancer and pancreatic diseases, this work demonstrates the feasibility of systematically screening a complex biofluid to reveal diagnostic markers and underscores the value of mouse models in identifying robust proxy biomarkers for human diseases. (*PLoS Med.* **5**, e123, 2008; doi:10.1371/journal.pmed.0050123) *PH*