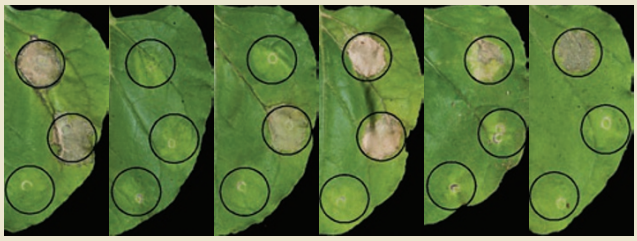
Potato blight genome



The fungus-like pathogen *Phytophthora infestans* is responsible for >$6 billion worth of losses annually in potato and tomato crops. By sequencing its ~240 Mb genome, Haas *et al*. reveal at least some of the secrets behind the oomycete's devastating success. The ~2.5-fold increase in size of the *P. infestans* genome relative to those of its relatives *P. sojae* (95 Mb) and *P. ramorum* (65 Mb) results not from a vast expansion in the number of protein-coding regions but instead from increases in the number of repetitive sequences. These account for ~74% of the genome and include a diverse range of transposons. A striking discontinuity in the distribution of relatively stable gene-rich regions and rapidly evolving gene-poor, repeat-rich stretches suggests that the latter may hold the key to the remarkable capacity of *P. infestans* to adapt to its host's defenses. Genes predicted to encode >500 RXLR and ~200 Crinkler cytoplasmic effector proteins, well known to facilitate oomycete colonization, typically occur in the repeat-rich regions where conserved gene order with *P. sojae* and *P. ramorum* is lost. Characterization of the members of these expanded protein families, using approaches such as the transient expression assay depicted, should shed light on how *P. infestans* outsmarts its hosts and suggest new ways to combat potato blight. (*Nature* **461**, 393–398, 2009) *PH*

Dendritic cell transcriptional networks

Unraveling the signaling pathways and gene expression programs involving Toll-like receptors (TLRs), which recognize molecules of pathogenic origin, is integral to our understanding host immune responses. Regev and colleagues use genetic perturbations to dissect the different transcriptional programs triggered in mouse dendritic cells in response to viral or bacterial pathogens. They knock down 125 candidate regulatory proteins with siRNAs and interpret the effects of these perturbations on the expression of 118 genes, thereby identifying a network of 2,322 regulatory interactions. Additional computational analyses identify core bacterial- and viral-response networks. Of particular interest, they validate a transcriptional circuit involving the chromatin modifier Cbx4, which resolves a long-standing mystery about how dendritic cells restrict secretion of interferon B1 in response to viral but not bacterial pathogens. This strategy demonstrates how to systematically map gene regulatory networks in primary mammalian cells. (*Science*, published online September 3, 2009; doi:10.1126/science.1179050) *CM*

Broadly neutralizing HIV-1 antibodies

Efforts to develop an effective vaccine against HIV-1 have been bedeviled by the diversity among the prevalent viral variants and the very limited number of broadly neutralizing antibodies (bNAbs) that target invariant portions of the spike glycoproteins gp120 and gp41. The best available neutralizing antibodies have limited potency, most notably against nonclade B viruses, which are also the most common variants in developing countries. Walker *et al*. tackle this challenge by screening sera from ~1,800 HIV-1 donors for broadly neutralizing activity and then narrowing the search for bNAbs by profiling the immunoglobulins produced by 30,000 activated memory B cells from a clade A–infected individual. This identifies two monoclonal antibodies, PG9 and PG16, which prevent infection in >70% of the 162 strains tested *in vitro* and display greater potency than previously described antibodies. Both bNAbs bind to a relatively invariant site on gp120 that seems sufficiently accessible to inform the design of immunogens for vaccination. Running neutralization assays instead of restricting the screen to antibody-affinity assays for coat proteins was key to this success: neither PG9 nor PG16 have strong affinity for the soluble recombinant versions of spike proteins used in previous screens. Instead, they seem to bind gp120 only in the context of trimeric gp120 and gp41 complexes. (*Science* published online September 3, 2009; doi: 10.1126/science.1178746, 2009) *PH*

Written by Kathy Aschheim, Markus Elsner, Peter Hare and Craig Mak

Targeting cancer stem cells

Cancer stem cells are thought to present a major problem for the complete eradication of cancer through their resistance to many standard treatments and ability to reestablish tumors. Now, Gupta *et al.* report they have found small-molecule drugs that specifically kill cancer stem cells among the other cells of a tumor. The authors identify such compounds using a high-throughput screen involving breast cancer stem cells and exploit the observation that the induction of epithelial-mesenchymal transition enriches for cells with stem-like properties. After confirming that cells that had undergone epithelial-mesenchymal transition after treatment with an E-cadherin short hairpin RNA (shRNA) have the hallmarks of cancer stem cells, they screen for drugs that specifically kill shRNA-treated cells. Their lead molecule, salinomycin, has a tenfold higher activity against the shRNA-treated cells than against cells treated with control shRNA. In breast cancer cell lines, salinomycin significantly reduces the percentage of cancer stem cells, whereas the commonly used drug paclitaxel (Taxol) increases it. *In vivo*, salinomycin inhibits the growth of xenograft tumors and reduces the number of metastases. (*Cell* **138**, 645–659, 2009) *ME*

Batten mice on the mend

In June, Palo Alto, California–based StemCells issued a press release on the results of a phase I clinical trial of human fetal neural stem cells to treat patients with infantile neuronal ceroid lipofuscinosis, a fatal neurodegenerative disorder commonly known as Batten disease. One-year follow-up data on six children were said to support the conclusion that the treatment, which involves injections of stem cells at multiple brain sites and immunosuppression, does no harm. In collaboration with academic scientists, the company has now published a related study of the therapy in a mouse model. Batten disease is a lysosomal storage disorder in which mutation of the lysosomal enzyme palmitoyl protein thioesterase-1 (PPT-1) leads to accumulation of intracellular lipofuscin, neuronal degeneration and early death. Transplantation of neural stem cells is meant to supply the missing enzyme to endogenous neurons as a secreted factor. The researchers transplanted $PPT1^{+/+}$ human fetal neural stem cells into the brains of neonatal immunodeficient $ppt1^{-/-}$ mice. Analysis near the end of the animals' lifespan showed restoration of PPT1 to 4.4–6.9% of normal levels and reduction of lipofuscin levels by >31%. The treatment also mitigated disease symptoms such as neuronal degeneration and loss of motor coordination. (*Cell Stem Cell* **5**, 310–19, 2009) *KA*