Cancer double punch

As pharmacological strategies become more complex, technologies that can deliver multiple compounds with fine temporal and spatial control are expected to improve clinical outcomes. A case in point is cancer treatments that combine antiangiogenesis drugs and conventional cytotoxic drugs. Coadministering these two kinds of agents has proved problematic, as inhibition of tumor vasculature can block the cytotoxic drug from reaching the tumor and can stimulate a hypoxic response that enhances the tumor's invasiveness, metastatic potential and resistance to chemotherapy. Sasisekharan and colleagues have designed a nanoscale particle that may offer a way out of this impasse. The particle rapidly releases an antiangiogenic drug in the tumor, ablating blood vessels and thereby trapping itself inside the tumor, and then slowly releases a cytotoxic drug, killing the tumor cells. A modified phospholipid vesicle, the particle consists of an antiangiogenesis drug (combretastatin-A4) encapsulated in an envelope that is conjugated to the cytotoxic drug (doxorubicin). The approach was shown to inhibit tumor growth and increase survival in animal models of melanoma and Lewis lung carcinoma. (*Nature* **436**, 568–572, 2005) *KA*

Prion hunters

New-variant Creutzfeldt-Jakob disease, a prion disease caused by consumption of meat from cows afflicted with 'mad-cow disease' or bovine spongiform encephalopathy, is readily detected in post mortem brain sections, but diagnosis from blood samples is not yet possible. Soto and colleagues have taken an important step toward this goal with an automated, sensitive assay for PrP^{Sc}, the abnormal prion protein that accumulates in diseased brains. The assay is based on the authors' previously reported "protein misfolding cyclic amplification" technology. In a manner analogous to PCR, the PrP^{Sc} signal is amplified through successive rounds of incubation with PrP^{C}, the conformationally normal version of the prion protein, resulting in conversion of PrP^{C} to PrP^{Sc}. After 140 cycles, the authors achieved a 6,600-fold increase in sensitivity over standard PrP^{Sc} assays. Application of this approach to the detection of PrP^{Sc} in blood samples of affected hamsters resulted in positive detection of the disease with an 89% sensitivity and 100% specificity. Further development of this technology may allow early diagnosis of prion diseases in humans and cattle. (*Nat. Med.* **11**, 982–985, 2005) *MZ*

Plants without the P

The value of grains as a nutrient source is tempered by the presence of phytates (inositol hexakisphosphates), which pose environmental and health problems. Grain-feeding animals, unable to metabolize phytates, release them into the environment, where they accumulate in water and cause eutrophication. Phytates also block the uptake of essential metals in people, particularly problematic with the grain-rich diets of the developing world. Now, Stevenson-Paulik *et al.* have created phytate-free *Arabidopsis thaliana* seeds, providing a model for generating better grains as well as for elucidating the poorly understood phytate biosynthetic pathways. After identifying two *A. thaliana* inositol polyphosphate kinases (AtIpk1 and AtIpk2), they studied the enzymes' *in vivo* effects in mutants with T-DNA insertions. Whereas these mutants show differences in concentrations of phytate intermediates in seed and tissue, development and seed yield are unaffected. One mutant grows poorly unless phosphate concentrations are reduced in the growth media, apparently owing to defects in phosphate sensing; this mutant was also unable to adjust root hair length according to exogenous phosphate concentration. These findings suggest that mutants in the pathway may be useful for developing more nutritious grain varieties. They could also further our understanding of the phosphate acquisition pathway in plants. (*Proc. Natl. Acad. Sci. USA*, **102**, 8454–8459, 2005) *LD*

Research Highlights written by Kathy Aschheim, Nadia Cervoni, Laura DeFrancesco, Gaspar Taroncher-Oldenburg and Mark Zipkin.

Doggy dog. Snuppy (Seoul National University puppy), the first-ever cloned dog, shown here with his biological father/twin. The cloned puppy is the product of somatic-cell nuclear transfer of skin cells from an Afghan male into oocytes from a female, also an Afghan. (*Nature*, **436**, 641, 2005)

Fingering out tumor progression

Identifying the genes that orchestrate tumor growth is a priority of cancer research. Barbas and colleagues have developed a screening method for discovering oncogenes and their targets using libraries of artificial zinc-finger transcription factors. Unlike other tools used to dissect gene expression, transcription factors can synchronously regulate multiple targets and can either activate or repress expression depending on their design. By screening cancer cell lines with artificial zinc-finger libraries, the authors identified an oncogenic transcription factor, TF 20-VP. Transduction of HeLa cells with TF 20-VP resulted in a phenotypic switch from a cell line that was drug-sensitive, poorly invasive and non-metastatic to one that was drug-resistant, highly invasive and metastatic. In addition, the transduced cells showed a greater propensity than non-transduced cells to invasiveness and metastasis in mice. Comparative gene expression analysis between cells expressing TF 20-VP and controls revealed strong overexpression of three cancer-associated genes, E48, AGT, IL-13Rα1, suggesting that they are upregulated by TF 20-VP. (*Proc. Natl. Acad. Sci. USA* **102**, 11716–11721, 2005 *NC*

Sequencing pyrotechnics

In a display of technical prowess, Margulies *et al.* have developed and implemented a parallel and easily scalable DNA sequencing system capable of reading 25 million bases, at 99% or better accuracy, in about 4 hours. This approximately 100-fold increase in speed over state-of-the-art Sanger sequencing rests on combining a novel fiber-optic slide of individual reaction wells, which allows parallel processing of approximately 1.6-million short DNA fragments, with bead-based pyrosequencing protocol, and with a set of algorithms capable of deconvoluting variable sequence signals within individual wells due to carry-forward and incomplete extensions. One of the main technical advances involves sample preparation. Random libraries of short DNA fragments obtained from shearing the genome are captured onto beads that are in turn emulsified and individually placed into reaction wells for amplification and sequencing, thereby eliminating the need to subclone each fragment. To determine the accuracy of their method, the authors carried out shotgun sequencing and *de novo* assembly of the *Mycoplasma genitalium* genome (0.58 megabase) with 96% coverage at 99.96% accuracy. Similar results were obtained for the 2.1-megabase genome of *Streptococcus pneumoniae*. (*Nature*, published online 31 July, 2005; doi:10.1038/nature.03959, 2005) *GTO*