Folate-fortified rice

Cereals such as rice, which constitute the staple in the diets of many people in developing countries, are poor sources of the essential B vitamin folic acid. Although mandatory industrial fortification has reduced the incidence of severe birth defects and other debilitating afflictions associated with folate deficiency, inadequate infrastructure in certain parts of the world makes biofortification an attractive alternative to supplementation with synthetic folate. Endosperm-specific overexpression of two *Arabidopsis thaliana* transgenes enables Van Der Straeten and colleagues to boost the folic acid content of rice grains up to 100-fold higher than levels in unmodified rice. Even after cooking, 100 g of the biofortified grains should meet the adult daily folate requirement. [**Brief Communications, p. 1277**] *PH*

Production of stable and effective bispecific antibodies

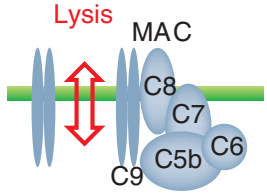
Bispecific antibodies that simultaneously inhibit two targets can provide better clinical efficacy than monospecific agents. However, most bispecific molecules are difficult to express and purify and have short half-lives in serum. Wu *et al.* develop bispecific antibody-based molecules, termed dual-variable-domain immunoglobulins (DVD-Ig), which can be purified from mammalian cells. The N-terminal portions of the heavy and light chains in these IgG-like molecules contain not one, but two, different variable regions fused in tandem by short linkers. Whereas the most N-terminal variable regions are derived from a monoclonal antibody against the first target of interest, the C-terminal variable regions and the constant regions are derived from a second monoclonal antibody with different specificity. Most DVD-Igs retain the physicochemical properties of the parental monoclonals. The authors show that an anti-IL-12/IL-18 DVD-Ig inhibits IL-12 and IL-18 as effectively as the parental monoclonal antibody cocktail. In a collagen-induced arthritis mouse model, another bispecific molecule, an anti-IL-1β/IL-1α DVD-Ig, is as active as the parental monoclonal combination therapy, despite a tenfold reduction in the affinity of the anti-IL-1α moiety compared to the parental monoclonal. In conclusion, as more and more monoclonal antibody treatments are being developed, this bispecific antibody platform might facilitate development of more complex therapy regimens.
[**Articles, p.1290; News and Views, p.1233**] *JWT*

Written by Kathy Aschheim, Michael Francisco, Peter Hare, Brady Huggett, Andrew Marshall & Jan-Willem Theunissen

Myxobacterial genome giant

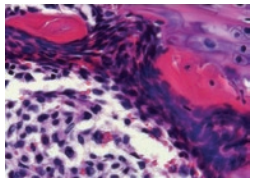
Müller and colleagues describe and analyze the genomic sequence of *Sorangium cellulosum* So ce56, which exemplifies its genus' morphological and physiological traits and produces several clinically relevant natural products, most of which are polyketides, nonribosomal peptides or hybrids of both. At 13 Mb, this is the largest bacterial genome sequenced to date and exceeds the size of the only other known myxobacterial genome by ~4 Mb. Although ~35% of the 9,367 predicted proteins it encodes have no similarity to predicted proteins, gene products with predicted functions in secondary metabolite synthesis and degradation of cellulose, hemicellulose and pectin show particular potential for expanding the biotechnological potential of this myxobacterium. Remarkably, 3.2% of the predicted coding sequences encode eukaryotic protein kinase-like kinases. Proteomic analysis underscores the importance of phosphorylation as a regulatory mechanism in *S. cellulosum*. [**Articles, p. 1281**] *PH*

Complement as a therapeutic target



As part of *Nature Biotechnology*'s 'case history' series, Russell Rother and colleagues discuss the discovery and development of the complement inhibitor eculizumab, a monoclonal antibody recently approved for the treatment of the rare hemolytic disease paroxysmal nocturnal hemoglobinuria (PNH). Somatic mutations in the phosphatidylinositol glycan–complementation class A gene in hematopoietic stem cells result in a deficiency of glycosylphosphatidylinositol-linked surface proteins, including the complement inhibitor CD59. Absence of CD59 triggers complement-dependent lysis of PNH red blood cells and chronic hemolysis can result in both severe anemia, requiring frequent blood transfusions, and thrombosis, the leading cause of premature mortality. The PNH clinical trials showed that eculizumab effectively reduces hemolysis, anemia, fatigue and thrombosis. In an accompanying review article, Daniel Ricklin and John Lambris provide an overview of complement signaling in innate and adaptive immunity and discuss five different categories of complement-based drug candidates: serine protease inhibitors, soluble complement regulators, therapeutic antibodies, complement component inhibitors and anaphylatoxin receptor antagonists. In summary, the recent approval of eculizumab validates complement as a therapeutic target and could facilitate development of new therapies for other complement-related pathologies, such as age-related macular degeneration, asthma and rheumatoid arthritis. [**Perspective, p.1256; Review, p.1265**] *JWT*

Leukemia stem cells



Ishikawa and colleagues describe a mouse model of human acute myelogenous leukemia that provides new insight into the leukemic stem cell that initiates the disease. Several immunodeficient mouse models, including the nonobese diabetic/severe combined immune deficient (NOD/SCID) mouse, have been used in the past to study human leukemia cells, but these models are not suitable for long-term experiments. The authors chose to investigate the NOD/SCID/IL2Rγ^{null} mouse because it has a long lifespan and is useful for studying human long-term repopulating hematopoietic stem cells. They show that this model, unlike the other immunodeficient models tested, allows efficient engraftment of human hCD34^{+}hCD38^{-} leukemic stem cells, engraftment in the peripheral blood as well as in the bone marrow, and long-term engraftment through serial transplantation to secondary and tertiary recipients. The model also reproduces key features of the disease, such as suppression of normal hematopoiesis. The authors find that leukemic stem cells home to the osteoblast-rich endosteal surface of bone—the niche of normal hematopoietic stem cells—and are more resistant to the anti-leukemia drug cytosine arabinoside than their differentiated progeny. [**Letters, p. 1315**] *KA*

Delivery of zinc-finger nucleases

Zinc-finger nucleases (ZFNs) catalyze double-stranded cleavage of DNA at specific sequences in the genome, thereby increasing the rate of homologous recombination at those sites with donor DNA molecules of similar sequence. Because they can be retargeted to new sequences of interest, ZFNs show promise as a therapeutic strategy for correcting disease-causing genes or introducing transgenes at chosen sites. Further development of this technology will require efficient and safe methods to deliver the required constructs (the donor DNA molecule and genes encoding two zinc-finger nucleases) into clinically relevant cells. With this goal in mind, Naldini and colleagues explore the use of integrase-defective lentiviral vectors for ZFN-mediated genetic modification of several human cell types, including cord-blood hematopoietic stem cells and embryonic stem cells. Efficient gene correction and site-specific gene addition are shown in the *IL2RG* gene using previously described ZFNs. The authors also use a new pair of ZFNs to target the *CCR5* gene—a possible 'safe harbor' for transgene integration—and demonstrate gene addition at this locus. [**Articles, p. 1298**] *KA*

Patent roundup

Is the US Patent Reform Act a plague on biotech? **[Editorial, p. 1187]** *AM*

A US Federal District Court in Boston ruled on October 23 that Roche's anti-anemia drug Mircera infringes an Amgen patent on pharmaceutical composition [**News in Brief, p. 1197**] *BH*

Patent thickets and freedom-to-operate issues may seem of little concern to noncommercial researchers, but academics may be more at risk than they realize. According to Yancey and Stewart, open-source solutions and open licensing from universities can minimize anticommons effects. [**Patent Article, p. 1225**] *MF*

Recent patent applications in drug discovery automation. [**New Patents, p. 1229**] *MF*

Palatable RNAi for insect control

Two groups show that engineering plants to deliver RNA interference (RNAi) in insect pests could potentially rival expression of *Bacillus thuringiensis* (*Bt*) insecticidal proteins as a transgenic strategy to protect crops from herbivory. Roberts and colleagues show that when included in an artificial diet fed to rootworm larvae, any of several insect-specific double-stranded RNAs (dsRNAs) cause stunting and mortality. This RNAi-associated effect is shared by at least two other coleopteran pests; indeed, a decrease in efficacy associated with target sequence divergence suggests that the approach might be used to avoid harming beneficial insects. Most notably, protection against damage by western corn rootworm (top image) in dsRNA-expressing corn plants was comparable to plants expressing a *Bt* protein. Chen and colleagues also observe the RNAi effect when cotton bollworms (bottom image) ingest leaf material from *Arabidopsis thaliana* or tobacco plants that express either of two dsRNAs. In a cunning strategy to home in on the Achilles heel of these devastating lepidopteran pests, they identify a cytochrome P450 that protects bollworms against gossypol, a toxin made by cotton plants. Ingestion of leaves expressing dsRNA specific for the P450 renders bollworms susceptible to gossypol. As this effect is not compromised in an *A. thaliana* mutant defective in dicing dsRNAs, it appears that the small interfering RNAs responsible for morbidity are generated by the insects after ingestion of unprocessed plant dsRNA. [**Articles, p. 1307; Letters, p. 1322; News and Views, p. 1231**] *PH*

Executable algorithms to mimic biology

On the basis of their distinction between so-called computational and mathematical models, Fisher and Henzinger define the emerging field of 'executable biology'. Because computational models—unlike their mathematical counterparts—prescribe an execution algorithm, they provide unique opportunities to mimic biological systems and can thus augment more conventional sets of differential equations, which are better suited to solving unknowns and analyzing relationships between quantities. Boolean networks, Petri nets, state-transition machines, process calculi and hybrids of mathematical and computational approaches are five approaches drawn from computer science that are proving their mettle in addressing challenging biological questions. These accomplishments are discussed in the context of the benefits of expanding the use of executable models in biological research as well as some challenges facing this trend. [**Review, p. 1239**] *PH*

Next month in nature biotechnology

- Focus on antivirals
- Potentiating a fungal insecticide
- Labeling of cellular receptor proteins with lipoic acid ligase