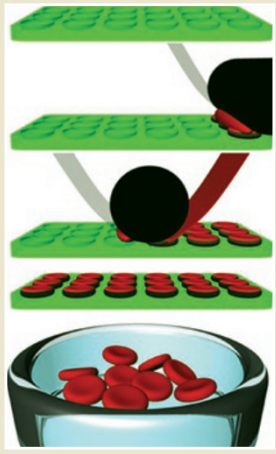
Stretching microparticle circulation



Micron-sized particles used for medical imaging or drug delivery are physically filtered out of the blood by the microvasculature of organs such as the lungs, liver and spleen. Merkel *et al.* show that making particles that mimic the ability of red blood cells to deform can extend their half-life in the circulatory system of mice. The authors mold hydrogel (red) into discoid-shaped particles using a template with wells (green) and a sheet of material (gray) that wicks away excess liquid from the mold surface, a technique they had developed previously. By varying the amount of cross-linker in the hydrogel from 1–10%, the authors create red blood cell–sized particles having an elastic modulus of 7.8–63.9 kPa. Mouse red blood cells have a modulus of 26 ±7 kPa. The authors observe that the most elastic particles had a half-life of >3 days when injected intravenously into mice, up to 30 times longer than the least elastic ones, as estimated by pharmacokinetic models and measured using blood draws. Although these studies highlight elasticity as a tunable parameter of microparticles, much work remains to reduce this observation to practical benefit. (*Proc. Natl. Acad. Sci. USA* **108**, 586–591, 2011) *CM*

Artificial proteins to the rescue

A new study asks whether the proteins constituting today's organisms are functionally optimal or whether unnatural diversity can be mined to find others that can substitute. To answer these questions, Fisher *et al.* construct a protein library of 1.5×10^6 proteins, each 102 residues long, that fold into alpha-helices, and test their ability to rescue *Escherichia coli* auxotrophs. Surprisingly, 15% (4/27) of the auxotrophs are rescued, and in all but one of these, more than one unnatural protein can substitute. Detailed analysis of the rescuing proteins shows that they fold as designed and have no natural homologs. The researchers eliminate several ways in which the synthetic protein might allow growth of the mutants (e.g., they direct the synthesis of the end-product, upregulate an endogenous *E. coli* protein that provides missing function or induce a stress response). How the synthetic proteins rescue the mutants, however, remains unknown; the authors cannot detect expected enzymatic activities *in vivo* or *in vitro*, which they attribute to low activity of the synthetic proteins. All rescued transformants grow less well than wild-type cells, suggesting that further selection might identify better-performing proteins. (*PLoS ONE* **6**, e15364, 2011) *LD*

On the trail of phytopathogen virulence

The expense caused by fungi and oomycetes to agriculture amounts to billions of dollars annually, in terms of both losses in yield and the need for pest management. Four recent papers use comparative genomics of agriculturally relevant oomycetes, smut fungi and powdery mildews to understand how these pathogens extend their host ranges. By enabling more effective ways to monitor pathogen adaptation to current control measures, these insights might open the way for more durable and effective strategies that can be incorporated into crop breeding and other pathogen control schemes to stabilize the global food supply. Understanding the modes of action of disease effector genes, which encode pathogen proteins that change plant responses to the pathogen in question, will likely be central to many such strategies. Working with four closely related *Phytophthora* species, Raffaele *et al.* note that most effector genes occur in gene-sparse regions, along with genes involved in epigenetic regulation. They postulate that the remodeling of chromatin structure may drive host adaptation, and that effector genes in more stable, gene-dense parts of the genome may be better targets for strategies aimed at sustained disease resistance. By comparing the genomes of the maize fungal pathogens *Ustilago maydis* and *Sporisorium reilianum*, Schirawski *et al.* identify regions of low sequence conservation, four of which define novel virulence determinants. Reports by Spanu *et al.* and Baxter *et al.* highlight unique features of the genomes of ascomycete mildews and oomycetes that have evolved obligate biotrophy, the complete dependence on living hosts for growth and reproduction. (*Science* **330**, 1540–1543, 1543–1546, 1546–1548, 1549–1551, 2010) *PH*

Redesigning recombinase specificity

Site-specific recombination enzymes, such as the Cre recombinase, have been widely used to manipulate genomic DNA, but the strict sequence specificity of existing recombinases limits their application to artificially introduced sites. More versatile so-called zinc finger recombinases (ZFRs) have been constructed by fusing zinc finger DNA-binding domains to the core catalytic domain of various recombinases. But these catalytic domains have their own sequence specificities, which limit the ability to functionally target ZFRs to new sites. In previous work, these intrinsic specificities have been simply relaxed, but a recent study by Gaj *et al.* shows that the catalytic domains can be engineered to target new sequences with high specificity. They identify potential DNA-recognition determinants in two recombinases and randomly mutagenize them. A screen for recombination events at a specific sequence identifies mutants with an up to 10,000-fold shift in specificity. The resulting ZFRs are shown to catalyze accurate insertion of a plasmid into a human genome. (*Proc. Natl. Acad. Sci. USA* **108**, 498–503, 2011) *ME*

GWAS for diagnostics

Prostate-specific antigen (PSA) is notoriously unreliable as a biomarker of prostate cancer. High serum PSA levels do not necessarily mean that a man has prostate cancer, and PSA levels can be low even when this cancer is present. PSA levels fluctuate in response to diverse factors, including inflammation, obesity, age and irritation of the prostate, and genetic differences are thought to account for 40–45% of the natural variability. Gudmundsson *et al.* propose to improve the utility of PSA screening by correcting for this genetic contribution. They perform a large GWAS study and identify six sequence variants associated with PSA levels, two of which are new and not associated with prostate cancer risk. Using data and prostate biopsies from thousands of men, they compare the ability of four models to diagnose prostate cancer: (i) PSA levels alone, (ii) PSA levels plus four sequence variants associated with PSA levels, (iii) PSA levels plus 23 sequence variants previously associated with prostate cancer risk and (iv) PSA levels plus all 27 sequence variants. The fourth model proves most accurate, suggesting that correcting an individual's PSA test result with genotype information would improve its diagnostic power. (*Sci. Transl. Med.* **2**, 62ra92, 2010) *KA*

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