as a minimal genome with a minimal set of genes[7]. Growth of *M. genitalium* (which has an 0.58-Mb genome) is much slower than *M. mycoides* (with a 1.08-Mb genome) or other mycoplasmas with larger genomes. The present protocol described by Gibson *et al.*[1] thus provides a useful system to understand how smaller sets of genes in different sets of combinations are essential for growth. If genes from other bacteria can be codon optimized to work in *M. capricolum*, ultimately the approach may also prove useful in assessing the functions of nonculturable microorganisms that are abundant in nature[8], for which we have growing sequence information. Indeed, one day it may be possible to use the system to study whole or partial plant or mammalian chromosomes.

Conversely, rather than investigating minimal synthetic genomes, it should also be possible to amend new genes to existing 'natural' genomes to design enlarged bacterial genomes. This raises a fundamental question of what is the largest size possible for a circular bacterial genome. In the Gibson *et al.*[1] protocol, the size of the synthesized genome is dependent on the largest molecule that yeast can handle. Work in our group[9] has begun to explore this in *Bacillus subtilis*. We have created a hybrid '*Cyanobacillus*' that stably possesses a 7.7-Mb genome through the addition of the *Synechocystis* genome (3.5 Mb) to *B. subtilis* (4.2 Mb)[9]. Addition of another genome (5.0 Mb) to our *Cyanobacillus* strain could potentially produce bacterial cells with genomes of 12.7 Mb—larger than the genome of yeast (12.5 Mb), which has one of the smallest genomes of the eukaryotes for which full genome sequences are available.

Ultimately, the importance of this breakthrough in synthetic biology will depend on further reductions in the cost of oligonucleotide synthesis, extensions in the size of artificial DNA molecules that can be constructed and demonstration that the principles described by Gibson *et al.*[1] for mycoplasmas can be applied more widely to other bacterial systems (e.g., *Escherichia coli*) more familiar to the biology and biotech research communities. Unlike the recent advance in which induced pluripotent stem cells were created from a small set of transcription factors[10]—a breakthrough which was almost immediately widely adopted across the research community—only a handful of laboratories around the world currently have the expertise and resources to carry out the kinds of experiments described by the JCVI group. The question is—with only a few groups around the world capable of working on this technology—how large a gap needs to be bridged between the mycoplasma genome described by Gibson *et al.*[1] and the many other genomes of biological interest?

COMPETING FINANCIAL INTERESTS
The author declares no competing financial interests.

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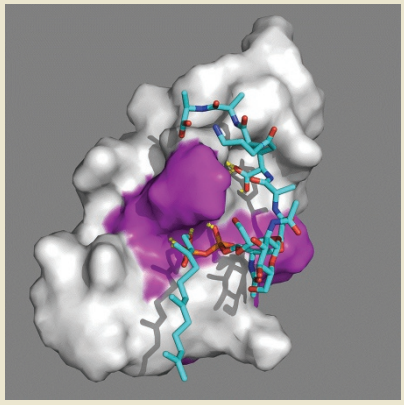
Antibiotic leads challenge conventional wisdom



Two recent papers in *Science*[1,2] provide surprising twists to the conventional views on how members of two extensively studied classes of molecules exert their effects. Whereas Schneider *et al.*[1] reveal a new mechanism of action for a subset of defensins, Wyatt *et al.*[2] show that certain nonribosomal peptides, a group of secondary metabolites most commonly regarded as antibiotics, might in fact be promising drug targets.

Defensins are a family of short antibiotic peptides conserved across the fungal, animal and plant kingdoms[3]. Whereas most defensins are thought to nonspecifically disintegrate bacterial membranes due to their amphipathic structures, Schneider *et al.*[1] show that the fungal defensin plectasin instead targets cell wall biosynthesis by sequestering the Lipid II precursor of the bacterial cell wall. At least four other defensins from fungi and invertebrates also inhibit the processing of Lipid II. Plectasin or improved plectasin derivates have previously been shown to be effective against multidrug-resistant strains of Gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus*. Remarkably, the antibiotic vancomycin—one of the few remaining drugs in our arsenal to treat multidrug-resistant Gram-positive infections—also binds and inhibits the processing of Lipid II. But fortunately, the authors observe no cross-resistance between vancomycin and plectasin and speculate that the distinct binding sites of the two molecules make the emergence of cross-resistance unlikely. Identification of a molecular target of plectasin may allow the rational design of improved variants and suggests that more rigorous scrutiny of the mechanisms of other defensins is warranted.

Nonribosomal peptides are a major class of bacterial secondary metabolites including—most famously—penicillin. Wyatt *et al.*[2] study the function of a nonribosomal peptide synthetase gene cluster that is conserved universally across *Staphylococcus aureus* strains, with orthologs in other pathogenic staphylococci. Although the products of the synthetase, two cyclic dipeptides named aureusimine A and B, are not required for growth, the expression of virulence factors is greatly reduced in their absence. *Staphylococcus aureus* strains without the nonribosomal peptide synthetase gene cause much milder infections in mice and are unable to colonize spleen, liver and heart. It remains to be seen whether investigation of the functions of other nonribosomal peptides might find similarly promising drug targets.

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