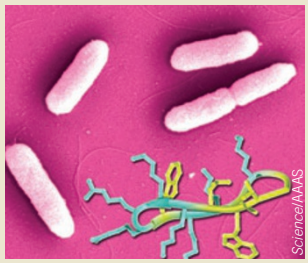
Peptidomimetic antibiotics against pseudomonas



The resistance of many *Pseudomonas aeruginosa* strains to frontline antibiotics complicates the management of hospital-acquired infections. Srinivas *et al*. describe a potential breakthrough in addressing this problem with the identification of a novel mode of bactericidal action. Starting from a cationic antimicrobial peptide, they perform iterative cycles of synthesis and screening of peptidomimetic variants to recover potent antimicrobial compounds. Nanomolar concentrations of two of the optimized compounds, POL7001 and POL7080, are active against the *Pseudomonas* species they test, but not against other bacteria. This selectivity may help to contain the emergence of resistant strains. Instead of lysing bacterial cells, the cyclic 14-amino-acid peptidomimetics appear to bind to and inhibit the outer-membrane protein LptD. This presumably interferes with LptD-mediated incorporation of lipopolysaccharide into the outer leaflet of the cell's outer membrane, a mechanism that does not appear to have been previously targeted in screens for antibiotic activities. Subcutaneous delivery of the compounds within 5 h of bacterial infection is more effective than gentamicin in a mouse model of septicemia. (*Science* **327**, 1010–1013, 2010) *PH*

Piecing together our gut microbiota

A consortium of scientists working under the MetaHIT (Metagenomics of the Human Intestinal Tract) project have sequenced ~577 billion bases of microbial DNA isolated from fecal samples of 124 people from Denmark and Spain. In contrast to previous studies of this kind—which sampled far fewer individuals, sequenced limited regions of DNA (such as the 16S ribosomal DNA) or took a mapping-based approach to match the sequenced fragments of DNA to known bacterial genes—this study used a *de novo* assembly algorithm to piece together billions of short (44 bp or 75 bp) reads into gene-sized stretches of sequence (N50 length of ~2.2 kb). In total, the assembled sequence contained ~3.3 million nonredundant open reading frames, which matched most of the genes of bacteria known to reside in the human gut and identified a core set of shared genes, bacterial species and gene functions present in the sampled individuals. The strategies described in this work for assaying the genetic content of many microbial communities in a deep, unbiased fashion should be useful for investigating questions of both basic research and applied biotechnological value. (*Nature* **464**, 59–65, 2010) *CM*

Tackling HIV's variability

The enormous sequence variety of HIV viruses has stymied vaccine development. A potential solution is the design of mosaic vaccines that maximize the sequence coverage of naturally observed sequence diversity. Barouch *et al*. and Santra *et al*. show that such vaccines can increase the breadth of epitopes that are recognized by T cells in nonhuman primates. Whereas Barouch *et al*. use replication-deficient adenovirus vectors to express mosaic genes for the HIV Gag, Pol and Env genes, Santra *et al*. use mosaic Gag and Nef genes encoded by naked plasmid DNA and vaccinia virus. In both cases, $CD4^+$ and $CD8^+$ T cells recognize a greater range of different epitopes as well as more variations of these epitopes than T cells in animals vaccinated with the consensus or wild-type sequences. Although more experiments will be needed to see whether the increased breadth and depth of the immune response will also be observed in humans and whether it translates into a better protection against viral challenges, the papers present further validation for the mosaic antigen strategy to deal with highly variable pathogens. (*Nat. Med.* **16**, 319–323, 324–328, 2010) *ME*

Written by Kathy Aschheim, Laura DeFrancesco, Markus Elsner, Peter Hare & Craig Mak

Family ties

The power of familial genomic studies is illustrated in two recent papers in which separate groups sequenced total genomes of multiple members of families with genetic disorders. Using Complete Genomics' (Mountain View, CA, USA) nanoarray sequencing platform, Roach and colleagues sequenced the genomes of two parents and two offspring, both of whom have two genetic disorders, Miller's syndrome and ciliary diskinesia. Looking at both parents and unrelated, affected individuals, the researchers were able to narrow down the critical gene to dihydroorotate dehydrogenase (*DHODH*) in Miller's syndrome and dynein axonemal heavy chain 5 (*DNAH5*) in dyskinesia. Analyzing the pedigrees allowed the researchers to determine that 70 new mutations arose per diploid genome, a mutation rate that differs from previous estimates. Meanwhile, Lupski and colleagues used the SOLID platform (Applied Biosystems; Carlsbad, CA, USA) to sequence ten family members of the first author, who along with three of his siblings, has Charcot-Marie-Tooth disease, a common neuropathy that has been associated with no less than 39 loci. Within those 39 loci, two mutations within a single gene, *SH3TC2* were present in all affected offspring, whereas the parents, as well as some of the unaffected offspring, had only one. Estimating the cost of these genomes is difficult due to fast-moving technological improvements; in the course of one of the studies, the yield increased by a factor of three. (*N. Engl. J. Med.*, published online, doi: 10.1056/nejmoa0908094, 10 March 2010; *Science*, published online, doi: 10.1126/science.1186802, 10 March 2010) *LD*

Giving stroma its due

Stromal cells in the tumor microenvironment modulate the growth characteristics of tumor cells and the efficacy of chemotherapies. Yet the assays and models used in cancer drug discovery do not generally consider tumor-stroma interactions, an omission that may help explain why drugs that appear promising in preclinical studies often fail in clinical trials. Mitsiades and colleagues propose to address this problem with an assay for screening potential cancer drugs in the presence of stromal cells. In their method, tumor cells are labeled with luciferase using retroviral vectors and cultured either with or without unlabeled stromal cells. The cells are then exposed to compounds, and the quantity of viable tumor cells is estimated from the bioluminescence signal. The authors tested a few tumor cell types against several thousand compounds. For more than half the compounds, the presence of stromal cells made the tumor cells less sensitive to the compound, and in a small fraction of cases, sensitivity was increased. These results suggest that including stromal cells in cell-based cancer screens could not only eliminate compounds from the discovery pipeline that would subsequently prove ineffective *in vivo* but also rescue promising compounds that would otherwise be discarded. (*Nat. Med.*, published online, doi:10.1038/nm.2112, 14 March 2010) *KA*