RESEARCH SNIPPETS FROM THE MEDICAL WORLD

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Once it was thought that *Mycobacterium tuberculosis* was genetically uniform. However, global surveys of clinical samples have shown that like other human-specific pathogens, it has a marked biogeography. A comparison of 90 genes in over 100 strains of the bacterium has established that the geographic variation has arisen as a consequence of human migrations over millennia – first by land out of Africa 50,000 years ago and then by sea back to Africa over the past few centuries – and subsequent genetic drift of Africa 50,000 years ago and then by sea back to Africa. It is not clear how *M. tuberculosis* tolerates the potentially deleterious consequences of genetic drift, but this cryptic variation will be taken into account in vaccine and drug design.

The pathogenesis of cystic fibrosis (CF) continues to be a topic of much debate. The lungs of patients with CF become colonized with antibiotic-resistant bacteria and the airways become blocked with mucus, alginate, and DNA. The DNA may be derived from bacteria or from the host, is highly anionic, and can act as a chelator of 

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\text{Mg}^{2+} \quad \text{and Ca}^{2+} \quad (\text{PLoS Pathogens} \ 4, \ e1000213,2008).
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At high concentrations, presumably in areas adjacent to the epithelium of the lung, DNA soaks up cations to cause gross membrane disruption and, thus, has a strong antimicrobial effect. Unfortunately, at lower concentrations, the DNA soaks up just enough cations to trigger signaling cascades that culminate in the addition of aminoarabinose to the surface lipopolysaccharide molecules of the major pathogen in CF, *Pseudomonas aeruginosa*. This renders the bacterium resistant to aminoglycoside antibiotics.

The need for new drugs to combat multidrug-resistant bacteria remains pressing. A recent study (Science 321, 1673–1675, 2008) found that a potent cell-division inhibitor, PC190723, exhibited strong antibacterial activity against *Bacillus subtilis* and *Staphylococcus* species *in vitro*. To determine the *in vivo* efficacy, mice were treated with a single subcutaneous or intravenous dose of PC190723, 1 hour after inoculation with a potentially lethal dose of *S. aureus*. Remarkably, all mice survived, in stark contrast to the death of all controls. Another study (Science 321, 1078–1080, 2008) examined the inhibition of microbial virulence, which is thought to present less selective pressure and, therefore, to reduce the likelihood of the development of resistance. Oral treatment with a virulence inhibitor, LED209, inhibited *Salmonella typhimurium* virulence gene expression in mice, when given before and after infection, with 80% of the treated mice remaining alive after 24 hours and 20% surviving up to 12 days. In contrast, all control mice died within 72 hours.

There is much talk about procalcitonin being the next big thing in the diagnosis of infective syndromes. A prospective observational study examining the test performance of procalcitonin for identifying serious bacterial infections in febrile infants or in infants ≤90 days of age without an identifiable bacterial source found that the mean procalcitonin levels for definite serious bacterial infections and definite plus possible serious bacterial infections were significantly higher than that for no serious bacterial infection. A cut-off value of 0.12 ng/ml identified all cases of bacteremia accurately. (*Pediatrics. 2008 Oct;122:4:701-10*). Procalcitonin measurements performed especially well in detecting serious occult infections.

Two African studies raise hopes that an effective malaria vaccine may be in sight (N. Engl. J. Med. 359, 2521–2532, 2008, and N. Engl. J. Med. 359, 2533–2544,2008). The vaccine, called RTSS, has been in development for more than two decades and may be more than 50% effective at preventing the disease in African children. The results are from phase II trials conducted at three sites in western Africa by the vaccine developer, GlaxoSmithKline (GlaxoSmithKline, London, UK) and a wide-ranging team of clinical, academic, and nonprofit funding partners. The next step will be phase III trials, which will scale up the numbers treated. These will be funded largely by the Bill and Melinda Gates Foundation in Seattle and will involve up to 16,000 children at 10 sites in seven African countries.

Bioinformatics algorithms are becoming increasingly successful for the functional annotation of genomes, but they cannot replace experimental approaches when searching for the highly specialized genes responsible for virulence in pathogens. Such approaches usually involve screening pathogens containing loss-of-function mutations, which can be both time consuming and fraught with ethical complications. A new alternative approach, called rapid virulence annotation, overcomes these issues by using convenient experimental organisms as surrogates for the mammalian immune system (Proc. Natl Acad. Sci. USA).
The genome of the pathogen is split into segments of around 40,000 bp and cloned into *Escherichia coli*. These modified strains are then screened for a gain in toxicity.

Microsporidia are obligate, intracellular parasites of animals, which makes them difficult to be cultured in the laboratory. Originally thought to be an ancient lineage of eukaryotes, owing to their lack of true mitochondria, they are now known to be related to fungi. Recent findings argue that synteny between the sex-determining locus of zygomycetes and a region in the microsporidian genomes confirm that microsporidia are true fungi and might undergo as-yet-unobserved sexual reproduction (Curr. Biol. 30 Oct 2008, doi: 10.1016/j.cub.2008.09.030). Whatever their sexual proclivities, their identification as true members of the fungal kingdom that are closely aligned with the Zygomycota will go a long way toward development of effective therapeutic strategies.

After years of disappointments, on the 9 February, 2009, an announcement was made of the first preliminary results of a trial in which a vaginal microbicide, Pro 2000, seemed to reduce human immunodeficiency virus (HIV) infection (Nature, published online 10 February 2009, doi:10.1038/news.2009.91). However, experts caution that the findings fall shy of being statistically significant. Definitive results will need to await the conclusion, later this year, of a much larger trial of the same microbicide, sponsored by the Medical Research Council in the United Kingdom. Pro 2000 is made by Indevus Pharmaceuticals of Lexington, MA, USA, and works by inhibiting HIV entry into cells.

Hypochlorite, the active ingredient in bleach, apparently kills bacteria and other microorganisms by unfolding essential proteins (Cell. Nov 14, 2008, 135:691–701). These findings help address questions about bleach from as long ago as the 1950s, when some microbiologists hypothesized that it disrupts the cell membranes. At low concentrations, hypochlorite recruits a chaperone protein, Hsp33, to protect bacterial proteins. However, at higher concentrations, hypochlorite overwhelms that effect and leads proteins to lose their three-dimensional structure and aggregate into insoluble clumps. Some of those proteins include enzymes of metabolic pathways, ribosomal proteins, and proteins involved in protein biosynthesis. Inactivating them, therefore, kills bacteria.

Sharing fecal matter may sound like the stuff of horror movies, but it has taken place for more altruistic reasons (Microbe, Feb 2009, http://www.asm.org/microbe/index.asp?bid=62803). Fecal “transplants” appear to be highly effective for treating individuals with multiple recurrences of *Clostridium difficile* infections and the procedure appears to “give back” to such patients “whatever was lost by antibiotic treatments.” The procedure entails instilling filtrates of fecal material harvested from a close relative or spouse by enema or gastric tube. Predictably, it is not performed often and it is difficult to get approval for the procedure. A carefully conducted clinical trial evaluating this procedure should provide interesting results.