nature immunology

Stepping up to the plate

Picking up where pharmaceutical companies have left off, new academic science coalitions are using innovative techniques to hunt for new antibiotics.

Recent reports of methicillin-resistant *Staphylococcus aureus* (MRSA) infections acquired outside of the hospital—'community-acquired MRSA'—make evident the urgent need to design new ways to combat this and other 'superbugs'. Although improved hygiene and stricter guidelines on overuse of antibiotics will aid in the avoidance of MRSA, new drugs will inevitably be needed to treat those who do become infected.

Unfortunately, the antibiotic development 'pipeline' is startlingly dry. Financial considerations have driven most large pharmaceutical companies to cease or substantially cut antibiotic discovery efforts. Typically used to treat acute rather than chronic conditions, antibiotics are prescribed (and, importantly, are purchased) in limited amounts. Adding to the economically unappealing characteristics of this drug class is its relatively short 'life cycle', limited in large part by acquisition of microbial resistance and by the increasingly stringent regulatory hurdles placed in the path of drug approval.

Many biotechnology company efforts to target microbial proteins not targeted by existing drugs failed at least in part because of a lack of confirmation of the physiological importance of those targets. Chemical 'tweaking' of existing antibiotics to improve functional properties continues, but efforts to develop compounds not resembling those to which bacteria are already resistant are rare.

Natural microbial products, the source of stalwart drugs such as streptomycin and penicillin, remain a potential reservoir of new antibiotics. Unlike synthetic compounds generated by combinatorial chemistry, natural compounds are 'selected by evolution' to function particularly well. In addition, some natural products (e.g., cationic peptides) 'multitask' by suppressing multiple microbial functions and are thus less likely to be easily 'bypassed' by resistant bacteria. Adding to the luster of natural products is the ability of some to boost innate immune defenses.

Recent findings further enhance the appeal of screening natural products. Metagenomics—sequencing of the collection of genomes present in a given environment—has identified an unanticipated diversity in microbe populations in soil and the human gut. In parallel, whole-genome sequencing indicates that even 'familiar' microbes from which antibiotics have already been derived contain genes encoding uncharacterized proteins.

Unfortunately, technical roadblocks stand in the way of harvesting this untapped store of natural products. So much of the microbial DNA amplified by metagenomic sequencing is unfamiliar in part because these 'mystery' microbes are refractory to traditional culture techniques. Experiments aimed at heterologous expression of DNA from previously uncharacterized microbes in easily cultured bacteria are underway. Efforts to culture unfamiliar microbes and to 'coax' well known bacteria to produce previously uncharacterized proteins are also in progress.

Although promising, these techniques need optimization, which, to for-profit companies, translates into a long wait before return on investment. Unlike biotechnology companies that often depend on investors with limited patience for the delay caused by lengthy research projects, large pharmaceutical companies often enjoy a steady stream of income and thus could better afford the time spent in long-term optimization work. However, the relatively small profit potential of antibiotics makes unlikely the re-entry of 'large pharma' into the antibiotic discovery arena. Organizations such as the Infectious Diseases Society of America are lobbying policymakers to enact financial incentives to entice 'large pharma' back (such as extended patents, orphan drug status and tax rebates). Whether these incentives will pass or be effective remains to be seen.

Meanwhile, academic scientists, a group accustomed to pursuing long-term investigations and unencumbered by profit considerations, have responded to the dry antibiotic development pipeline by forming multidisciplinary initiatives. At Harvard, the Microbial Sciences Initiative, by funding fellowships, hosting seminars and offering new microbiology courses, aims to exploit the potential of microbial products.

After a 2005 workshop, the Canadian Institutes for Health Research kicked off a 5-year funding blitz with CA$10 million in grants offered to investigators searching for new alternatives to antibiotics. Work focusing on 'outside-the-box' treatments, including the manipulation of innate immunity, as well as phage and antibody therapy, was funded.

At the University of California San Diego, investigators looking farther afield to the microbial flora in the depths of the ocean have partnered with scientists in the schools of medicine, chemistry and pharmacy. By harnessing their vast 'in-house' expertise, this coalition hopes to guide promising leads from discovery through preclinical and even clinical testing.

Although free of profit considerations, such coalitions require funding. Encouragingly, the National Institutes of Health has launched the Drug Discovery and Mechanisms of Antimicrobial Resistance study section and stands behind the Strategies to Address Antimicrobial Resistance Act. Recently proposed by a bipartisan congressional team, this act will in part fund research into new antibiotics. Universities and biotechnology companies have also offered funding to these academic coalitions.

What else can be done? As noted at the 2005 Canadian Institutes for Health Research workshop, although invited to attend, immunologists were conspicuously absent. New data indicating that MRSA directly attacks neutrophils should make obvious the potential value of immunological expertise for antibiotic discovery efforts. Involvement of immunologists need not stem solely from altruistic reasons, however. MRSA could provide a new host-pathogen model system from which knowledge about immune defense mechanisms might be gained, and collaborations with microbiologists could provide much-needed lab funding. Regardless of the reason, immunologists' participation in efforts to identify new strategies to fight MRSA would no doubt be welcome.