MRSA is merciless

The pandemic flu, due to a novel influenza virus A(H1N1) spreading across the globe, has sidelined a life-threatening bacterial infection that has been spreading quietly for some time. A recent article[1] reports that millions all over the globe are battling a nosocomial MRSA, acronym for methicillin-resistant *Staphylococcus aureus*. In 2007, the Centre for Disease Control reported that MRSA causes 19,000 deaths every year in the US, which is more than HIV/AIDS cases. Almost 20% of people who contract MRSA are reported to die from it, and an increasing number of its victims are young. A 12-year-old boy in Michigan, USA, died after a wound he received on the basketball court, became infected with a bacterium that has become resistant to one of the most potent drug classes in the current antibiotic arsenal. Other similar stories can be found. Methicillin, a derivative of the better-known penicillin, was introduced in 1959 to treat infections caused by bacteria such as *Staph. aureus* and *Streptococcus pneumoniae* – that have become resistant to penicillin. European hospitals, however, observed methicillin-resistant strains of *S. aureus* just two years later, and by the 1980s MRSA had become widespread in hospitals throughout the world, including Siberia and India.

No one knows for sure how MRSA originates. *S. aureus* or *S. pneumoniae* are not some unusual bacteria found only in hospitals. The large majority of antibiotics currently used for treating infections and the antibiotic resistance genes acquired by human pathogens, each have an environmental origin[2]. These have been isolated from normal human beings, prompting the question 'how do new strains resistant to existing antibiotics originate'? It might well be that with the competing antibiotic sensitive bacteria kept relatively low in the disinfected hospital surroundings; the resistant bacteria that do arise have a free run of the place and the body. Resistance originates through mutations arising in one of the bacterial genes responsible for an enzyme that the bacterium normally produces as a chemical weapon to degrade a variety of toxic compounds in its environment to promote its own survival. The resistant genes can be swapped with harmless bacteria in the environment in what is called horizontal gene transfer, rendering them resistant and so the process goes on; the numbers of drug-resistant bacteria increase. Or, if the resistance factor is on a plasmid and the bacteria indulge in sexual reproduction. Walsh and Fischbach[1] witnessed in action the process of horizontal gene transfer when MRSA, VRSA (vancomycin-resistant *S. aureus*) and a third bacterium, *Enterococcus faecalis*, were isolated from the same dialysis patient in a hospital in Michigan, USA, in 2002. The origin of multiple drug resistant bacteria has been known for some time. Genetic analysis of these strains showed that a plasmid (a circular DNA molecule living extrachromosomally in bacterium) containing the vancomycin-resistant gene cassette (along with resistance genes for three other antibiotics and one class of disinfectants) had been transferred from *E. faecalis* to MRSA, creating a novel strain VRSA. Since vancomycin is the antibiotic of the last resort, rise of MRSA is bad news.

Walsh and Fischbach[1] point out that when MRSA or other resistant bacteria cause pneumonia, an already bad situation becomes more lethal. They write: 'with the rise in resistance that inevitably follows the clinical deployment of an antibiotic, there is a continual need for new antibiotic discovery, development and approval'. Food and Drug Administration approvals for Synercid (quinupristin/dalfopristin) in 1999, Zyvox (linezolid) in 2000 and Cubicin (daptomycin) in 2003 have addressed life-threatening infections from drug-resistant Gram-positive bacteria such as *S. aureus*, *S. pneumomiae* and *Enterococcus faecalis*. However, because these antibiotics are not active against an emerging class of nosocomial (hospital-acquired) pathogens (multidrug-resistant Gram-negative bacteria, including strains of *Klebsiella*, *Acinetobacter* and *Pseudomonas*) there is renewed focus on developing treatments for infections caused by Gram-negative bacteria. There is also a desperate need of new antibiotics – chemicals that will selectively kill the bacteria, leaving the eukaryotic cell. The first few cases of MRSA from India were reported in 1996.

An intensive search has already been made by the drug companies for new microorganisms as sources of new antibiotics. Organic chemists have synthesized thousands of compounds, many of these are yet to be tested for antibacterial activity. The Pfizer company in USA has a library of some 1.6 million compounds. They have discovered a promising class of potent antibacterials with a previously undescribed mechanism of action[3]. For example, in bacteria, the pyridopyrimidines target the ATP-binding site of biotin carboxylase (BC), which catalyses the first enzymatic step of fatty acid biosynthesis. These inhibitors are effective *in vitro* and *in vivo* against fastidious Gram-negative pathogens including *Haemophilus influenzae*. Although the BC active site has architectural similarity to those of eukaryotic protein kinases, inhibitor binding to the BC ATP-binding site is distinct from the protein kinase-binding mode, such that the inhibitors are selective for bacterial BC. The authors point out that it remains to be seen if the huge array of eukaryotic inhibitors present in pharmaceutical laboratories can be mined for their activity against structurally related bacterial targets such as the bacterial histidine kinases involved in cell–cell signaling, lipopolysaccharide sugar kinase involved in Gram-negative cell wall formation, antibiotic kinases that deactivate specific antibacterial agents, or less obvious targets, such as biotin carboxylase. The trick is to find some essential step in bacteria, such as in energy production pathway, distinct from that in eukaryotes and use it as a target for anti-infective strategy. Here, the bacterial genomics has promise. Most microorganisms use a biosynthesis pathway encoded by the *men* genes to produce menaquinone, a molecule needed for bacterial anaerobic respiration[4]. Until some new antibiotic is discovered, one obvious way to meet the challenge of MRSA infection rates is stricter precautions in hospitals and proper disposal of medical wastes[5].

1. Walsh, C. T. and Fischbach, M. A., *Sci. Am.*, July 2009, 44–51.
2. Martínez, J. L., *Science*, 2008, **321**, 365–367.
3. Miller, J. R. *et al.*, *Proc. Natl. Acad. Sci., USA*, 2009, **106**, 1737–1742.
4. Hiratsuka, T. *et al.*, *Science*, 2008, **321**, 1670–1673.
5. http://en.wikipedia.org/wiki/MRSA