Antibiotic Discovery: A Step in the Right Direction

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A group of Merck scientists in the United States and Spain have now come up with a very clever screening technique and discovered an unique antibiotic (Phillips et al., 2011). Such discoveries are sorely needed to assist us out of the antibiotic crisis that the world is now experiencing.

The world is in dire need of new antibiotics (Spízek et al., 2010). It is encouraging that a new class of antibiotics, represented by kibdelomycin, is still being discovered in the face of the antibiotic crisis that exists today globally. Infectious disease is the second most important killer of humans in the world. About 17 million people die each year as a result of bacterial infections (Butler and Buss, 2006). Not only are we battling the increase in antibiotic resistance in known pathogens, but there are at least 30 new bacterial and viral diseases that have emerged since the 1980s. However, despite this, most of the international pharmaceutical industry is moving away from antibiotic discovery (Demain, 2002). Large pharmaceutical companies that have dropped or significantly reduced research on antibiotic discovery include Merck, Wyeth (now part of Pfizer), Aventis, Eli Lilly, Abbott Laboratories, Bristol-Myers Squibb, and Schering-Plough (now part of Merck) (Barrett, 2005). This is easily seen by the drop in the number of approvals of new antibiotics by the regulatory agencies. New antimicrobial approvals, which were commercialized between 1983 and 1987, amounted to 16. In the period of 2003-2007, this had dropped to five, and the numbers from 2008 to 2010 were down to two. Much of this is caused by the increased difficulty in isolating novel drugs, including antibiotics. Factors that have affected the discovery of all drugs include "merger mania" in the industry, the increased development time and cost for clinical trials, the shift away from natural product discovery in favor of combinatorial chemistry, genomics and proteomics, and the decreases in research and development spending by the industry since 2001, due to the movement of industry funds from research to the promotion of already known drugs. For instance, in 1991, the amount spent by the pharmaceutical industry to market, promote, and advertise their products was 9.2 billion dollars. By 2004, this amount had increased to 25 billion dollars, mainly due to direct advertising to consumers, free drug samples, and salaries for drug representatives.

In this issue, a novel screening technique is described that was used by scientists at Merck & Co. in the United States and Spain to come up with an exciting new antibiotic called kibdelomycin (Phillips et al., 2011). This novel compound, produced by *Kibdelosporangium* sp, is a potent inhibitor of bacterial type-II topoisomerases, preferentially inhibiting the ATPase activity of DNA gyrase and topoisomerase IV. As a result, it has broad-spectrum activity against Gram-positive bacteria such as *Staphylococcus aureus* (MRSA), *Streptococcus pneumoniae, Enterococcus faecalis,* and *Bacillus subtilis*, and also is active against the Gram-negative *Haemophilus influenzae* (Phillips et al., 2011). It is the first potent inhibitor of bacterial type-II topoisomerases discovered in the last 60 years, and does not show cross-resistance with other gyrase inhibitors. Its mechanism of action is similar but not identical to that of other gyrase inhibitors, such as the coumarin antibiotics novobiocin and coumermycin A1 and the fluoroquinoline antibacterial ciprofloxacin. However, kibdelomycin is active against novobiocin-resistant and coumermycin-resistant strains of *S. aureus*. It is also active against the *S. aureus* strain that is resistant to ciprofloxacin. The chemical genomics profiling method used for the discovery of kibdelomycin is based on the previously developed *S. aureus* fitness test (SaFT) (Donald et al., 2009; Huber et al., 2009) and represents a highly powerful tool for the discovery of new natural products that is capable of predicting the mode of action of the compound discovered.

The discovery of kibdelomycin gives us hope that it will stimulate the industry to return to the antibiotic area by use of intelligent assay procedures that are capable of being used in a high-throughput manner, thus facilitating the identification of novel bioactive compounds.

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