COMMENT

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The golden age of antibiotic discovery began with systematic testing of soil microbes by Selman Waksman (pictured centre).

Recover the lost art of drug discovery

Bacterial evolution is overwhelming our antibiotic defences, says **Kim Lewis**. Using modern technology to replicate past success might tip the balance in our favour.

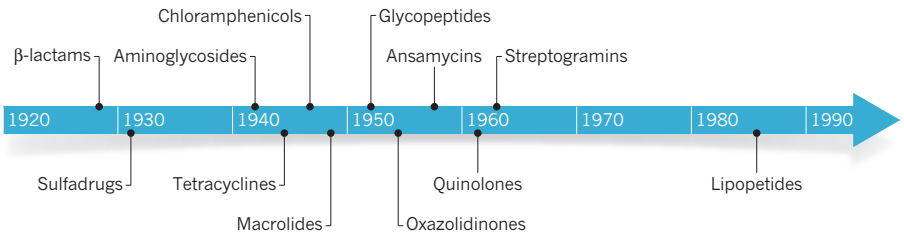
The more we know about antibiotics, the fewer we can discover. This is essentially why the field is in trouble — only one antibiotic belonging to a new class, the narrow-spectrum daptomycin, was discovered and made it into clinical practice in the past 50 years. After decades of little success, pharmaceutical firms are pulling the plug on antibiotic discovery. Most have either left the field (such as Merck, based in New Jersey, and Eli Lilly in Indiana) or are downsizing their effort. But the spread of antibiotic-resistant pathogens continues unabated[1].

Advances in medicine have exacerbated the problem. Clinicians are struggling to treat infections that tolerate antibiotics, in which bacteria produce a small quantity of dormant, spore-like persister cells[2]. The only function of dormant persisters is survival; once the antibiotic concentration drops, persisters wake up, start propagating and the infection relapses. Although this type of infection is rare in healthy individuals, whose immune cells can effectively kill both growing and dormant persister cells, it has become an increasing problem as a side effect of medical intervention. Cancer chemotherapy and transplant drugs, for instance, weaken the immune system, and artificial devices — catheters, heart valves and orthopaedic implants such as hip joints — are ideal platforms on which biofilms can form. Immune cells cannot penetrate these mats of bacteria, so they become a protective habitat for dormant persisters.

The increase and spread of antibiotic-resistant pathogens — which have evolved resistance mechanisms against specific drugs — is another cause for alarm[3]. Given the ▶

ANTIBIOTIC DISCOVERY TIMELINE

Decades without identifying antibiotics that go on to be used for the treatment of patients has put our defence against bacteria at risk. This timeline pinpoints the year that the antibiotics were first discovered.



lack of new antibiotics, we are in a stand-off with human pathogens. And we are poised to lose, prompting a return to the pre-antibiotic era of epidemics. Several human pathogens have already produced globally resistant strains, such as *Acinetobacter baumannii* that causes non-healing wounds, and some strains of tuberculosis (*Mycobacterium tuberculosis*). Although these pathogens represent only a tiny proportion of the bacteria out there, resistance is increasing. For example, highly resistant strains of the superbug MRSA (methicillin-resistant *Staphylococcus aureus*) were initially restricted to hospitals, but are now widely present in the community.

Why did we lose the ability to discover antibiotic compounds? I think that we should look to the golden era of discovery, in the middle of the last century, and revive what worked then. Several approaches were successful in the past but were abandoned, each for its own reason. However, these can now be revitalized using modern tools and expertise. Now is the time to recover the lost art of antimicrobial drug discovery.

RETURN TO OUR ROOTS

Following the discovery of penicillin in 1928, the golden era for finding new antibiotics really began in the 1940s, when microbiologist Selman Waksman exploited bacteria's ability to produce their own antibiotics (which they use to out-compete each other) by systematically testing soil microbes — largely streptomycetes. This led to the discovery in 1943 of streptomycin, the first antibiotic used to treat tuberculosis. The method that Waksman used — an approach I will refer to as the Waksman platform — was widely adopted by the pharmaceutical industry and yielded the main classes of antibiotics over the following 20 years (See 'Antibiotic discovery timeline'). But despite years of success, this overmining of soil bacteria resulted in diminishing returns — the same compounds were continuously found, and the platform collapsed.

This period also saw the identification of the main classes of synthetic compounds, but only a single broad-spectrum class — the fluoroquinolones — was introduced in the 1970s and 1980s. The main reason why so few synthetic compounds work is because they cannot penetrate the bacterial cell envelope. Scientists can identify antimicrobials from screening, or by designing compounds that fit into active sites of bacterial enzymes and inhibit their functions, but they cannot cross this formidable barrier.

More than a decade ago, medicinal chemist Christopher Lipinski found a way to circumvent another problem that was plaguing drug discovery: how to find compounds that could be absorbed well by the human gastrointestinal tract, making them available for oral use. With his team, Lipinski culled information from hundreds of approved drugs and came up with a list of five properties (such as size and water-repellent nature) that made compounds more prone to absorption. Since then, chemists have synthesized compounds using the Lipinski rule of five to ensure that they can be taken orally. I believe that we should do the same for antibiotics, by developing 'rules of penetration' that enable antibiotics to break through the sturdy bacterial cell envelope. The number of known molecules that penetrate well into bacteria is very small, not enough to form a set of rules, but we can measure how well compounds from a collection of randomly selected chemicals enter bacteria, rank these, and deduce the desirable properties for penetration. Knowing these rules should then enable us to build focused libraries of compounds that are likely to reach their targets in bacterial cells.

OLD IDEAS

We should also revive the approach that allowed the discovery of several compounds in the 1950s that were effective against *M. tuberculosis*. At that time, tuberculosis was still a major cause of death in the Western world, and to identify treatments, scientists screened synthetic compounds against *M. tuberculosis*, discovering isoniazid, pyrazinamide, ethionamide and ethambutol. Now, researchers screen libraries to identify compounds that work against many different pathogens, and those compounds are much harder to find. Therefore, unsurprisingly, since the four synthetic compounds specific to *M. tuberculosis* were identified no others have emerged despite researchers screening a thousand times more molecules when the global library increased to more than ten million compounds. Although physicians will always need broad-spectrum antibiotics, they could also use targeted compounds, particularly since the rapid diagnosis of the pathogen causing an infection is becoming available. This would allow selective therapy, using a pathogen-specific compound that will leave the body's natural protective flora untouched.

In addition, scientists should attempt to synthesize 'prodrugs' again. First discovered in the 1950s, these compounds are harmless until they enter a bacterial cell, at which point an enzyme converts them into a toxic substance, with properties similar to bleach. Prodrugs can kill both growing and dormant cells, suggesting that they could be effective against the seemingly invincible persister cells that make infections so difficult to treat. In the 1960s, reasoning that compounds without specific targets might be toxic, scientists began testing all compounds to see if they hit specific targets in bacterial cells. However, this resulted in the discarding of prodrugs, which do not have specific targets, just general toxicity to bacteria once converted. This explains, at least in part, why the discovery of synthetic compounds, many of which are prodrugs, ceased in the 1960s. I think that we should look again at prodrugs, because they may be a powerful weapon against both relapsing and untreatable chronic bacterial diseases.

Finally, we need to revive the Waksman platform. We stopped discovering useful classes of antibiotics from soil bacteria decades ago, but that was during a time when it was impossible to culture most (more than 99% of) bacterial species. Today, methods to culture these microbes are being developed, providing access to chemical diversity that was previously missed[4]. Examining the gene-expression patterns of the bacteria exposed to newly isolated antibiotics and comparing these with the characteristic expression profile of known antibiotics might avoid 'rediscovering' penicillin or streptomycin. A new pattern of gene expression will suggest a new compound, and could even point to its target.

Opportunities for antibiotic discovery are certainly there. What is not known is how effectively we will take advantage of them. ■

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