The Time for Breakthroughs in Antibiotics: 10 Biotech Startups Fighting Bacterial Resistance

Oct. 11, 2016 by Andrii Buvailo

Since a revolutionary discovery of penicillin in 1928 by Scottish bacteriologist and Nobel laureate Alexander Fleming, numerous inventions of new antibiotic classes followed. A cascade of discoveries over decades pushed the limits of medicine in its ability to fight deadly infections, those that used to kill millions of people in the previous centuries.

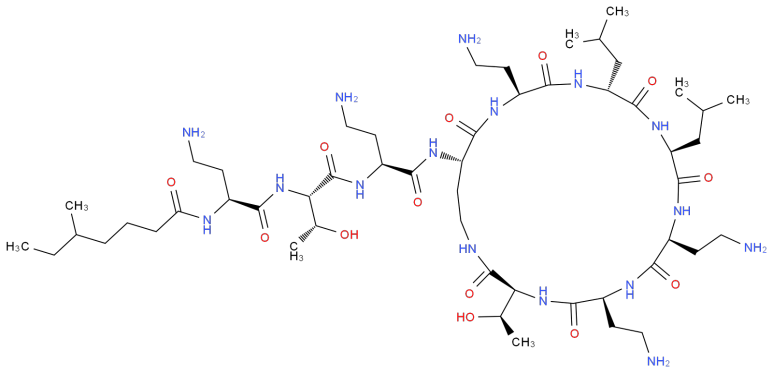
A today's slow catastrophe

We have been successfully using antibiotics in so many cases and for such a long time that started taking this powerful tool of modern medicine for granted. Meanwhile, the first warning signs started making headlines informing the public about emerging "superbugs" able to withstand antibiotics due to developed multidrug resistance and thereby becoming a deadly risk.

The dangerous infection MRSA (methicillin-resistant Staphylococcus aureus) was reported spreading in hospitals and healthcare facilities, while uncontrolled overuse of antibiotics in livestock farming led to the emergence of new resistant strains of bacteria such as Salmonella and E. coli. These are just examples, the list can go on.

According to the statistics from The Center of Disease Control and Prevention in the United States (the CDC), around 2 million people are infected by antibiotic-resistant illnesses in America alone, of whom around 23,000 die each year because antibiotics simply don't work as they used to in the not-so-distant past.

As widely used therapeutics such as tetracycline, erythromycin and vancomycin lost much of their effectiveness against bacterial infections over the years, the antibiotics Colistin and Carbapenem are considered the big guns — a last line of defense when no other antibiotics are working.



Colistin structure

Such medications are called drugs of last resort and they usually possess drastic side effects, as in the case of Colistin, being toxic to the human kidney; still, they are the last hope for some desperate patients. Now even this last weapon against malicious bacteria is becoming obsolete, as in recent months mcr-1, a gene which confers resistance to Colistin, has been found in E.coli from over 30 countries, including the cases of resistant bacteria isolated in China and in the United States.

The same story happens in the case of Carbapenem when the gene blaNDM-5 renders bacteria resistant to its action. In 2012, the CDC identified Carbapenem-resistant infections in about 4 percent of US hospitals.

The problem goes beyond treating infections. According to Army Col. Emil Lesho, director of the Defense Department's Multidrug-resistant Organism Repository and Surveillance Network in the United States, the growth of bacterial resistance puts humanity at risk of losing access to modern medical "miracles", such as medical surgeries, joint replacements, organ transplantation, cancer chemotherapies etc. These treatments can not be safely performed without antibiotics because it is almost impossible to avoid bacteria penetrating the body during severe medical interventions.

Why has the crisis begun?

The history of antibiotics research is the history of a constant race between drug discovery researchers and ever-evolving natural enemy - bacterial infections. Since the discovery of early antibiotics, it was noticed that bacteria would evolve rather quickly adjusting to the new environment and developing resistance to external molecules. Once resistance was developed rendering the existing antibacterial drug useless, a new type of antibiotics was needed to save the day.

Drug discovery industry used to do a good job at keeping up with natural bacterial threats and numerous new classes of antibiotics were discovered in the mid of the last century. However, the progress slowed down and almost vanished by the 2000s. In fact, researchers haven't identified a new class of antibiotic medication since 1987, while bacteria kept developing resistance to the previously invented drugs. So why has innovation stopped?

There are several reasons why big pharma companies largely abandoned the area of antibiotics research leaving it high and dry for more than 25 years.

One aspect of the problem is that antibiotics are extremely difficult to be developed as all "low hanging fruits" were already picked at the time of "golden age" of antibiotics in the 1940s, 50s, and 60s. Now science has kind of a "lottery approach" to developing new antibacterial drugs: some research groups accidentally come across an interesting candidate and try to develop it, usually, with very low success rates. In order to increase productivity, it is essential to develop platforms that provide a foundation for antibiotic discovery and allow researchers to identify large numbers of potential candidates. Without substantial choice of lead compounds, there is nothing for drug discovery researchers and pharma companies to test and refine for human trials.

But here is **another and a bigger part** of the problem: the economics of drug development. Pharmaceutical companies spend hundred of millions of dollars on drug discovery research, multi-step clinical trials and the FDA approval process, thus, the result has to pay back very well, for a long time and with minimum business risks.

It stimulates companies concentrate on therapeutic areas where there are chances to develop blockbuster drugs. An ideal candidate would be demanded by millions of people on regular bases for a very long period of time, like pills to keep cholesterol in check, or normalize blood pressure or maintain sexual life active.

This is where antibiotics are among the worst candidates.

They have strict prescription limits and should only be used for about a week. They are relatively cheap, for example, compared to anti-cancer drugs, and worst of all, they compete in a field of inexpensive generics making it hard to gain profits. On top of that, antibiotics can become obsolete at any time due to developed bacterial resistance and this is a substantial risk for business.

According to Dr. Anthony Fauci, director of the National Institute for Allergies and Infectious Diseases in the United States, without government policies encouraging investment in antibiotics development, “there’s very little incentive” for pharmaceutical companies to go this way.

The third problem is of social nature and it is a widely practiced overuse of antibiotics both in medical organizations and in agriculture. It gives bacterial organisms more chances to develop resistance and accelerates emergence of multidrug-resistant “superbugs”.

Reviving the lost art of antibiotics discovery

It wasn’t long ago that the landscape of antibiotics research was barren of fresh ideas and promising startups. But when it became apparent that the new antibiotics crisis had the potential to pose a serious threat to public health on a global scale, action followed on the side of government authorities.

In 2012, the United States administration introduced the Generating Antibiotics Initiatives Now (GAIN) Act, which provides substantial incentives for pharma businesses and investors to play the game of antibiotics discovery. The Act extends the exclusivity of new antibiotics by five years over any existing exclusivity, such as the ongoing patent protection, Hatch-Waxman, orphan drug or pediatric exclusivity. It gives extra-time for pharmaceutical companies to market antibiotics without the need to compete with generics. In addition, all new antibiotics that fall under the GAIN provisions receive fast track and priority review status which substantially accelerates the approval process with FDA.

With new incentives from government, big pharma tiptoed back pouring money into antibacterials industry and a wave of fresh startups developing antibiotics is rising.

Several examples of recently emerged companies with focus on promising antibacterial therapeutics include: Macrolide Therapeutics which raised $22 million from GlaxoSmithKline, Novartis and Roche; Iterum Therapeutics with its recent $40 million series A round; Spero Therapeutics and its $30 million round B this year; Cidara Therapeutics with $42 million round B last year and underwritten public offering of its common stock announced recently; and Entasis Therapeutics, a spinout of AstraZeneca, which snagged $50 million for its antibacterial research.

Overall, several antibiotics have been approved recently by FDA. In the area of Gram-positive infections, two new glycopeptides, Dalbavancin (Dalvance©, Xydalba©), Oritavancin (Orbactive©), and one new oxazolidinone Tedizolid (Sivextro©) offer alternatives to the already available choices. In the Gram-negative area things are moving slower with only two new cephalosporin-beta-lactamase inhibitor

combinations approved by FDA, Ceftobiprole (Zevtera©, Mabelio©) and Ceftolozane-tazobactam (Zerbaxa©), differentiating only in their activity on a molecular level of specific resistance mechanisms.

Teixobactin - a game-changing breakthrough

Among all things happening now in the field of antibiotics discovery one breakthrough should be given particular attention to, since it might change a paradigm of antibiotics development for the next several decades, overcoming the problem of bacterial resistance.

A year ago, a group of scientists led by Dr. Kim Lewis, Director of the Antimicrobial Discovery Center at Northeastern University, reported a new antibiotic, teixobactin, able of killing several types of bacteria, including antibiotic-resistant strains of tuberculosis and staphylococcus (MRSA infections) without detectable resistance developing over time. Teixobactin is a small molecule antibiotic of a new class - the world's first known medication capable of destroying 'drug resistant' bacteria.

What is even more groundbreaking is a way by which the compound has been found. Researchers developed an innovative reinvention of an old technique used in the past for many of the antibiotic discoveries of the mid-twenties century - from soil samples.

Combing soil samples for microbes producing their own antibiotic compounds to kill competing bacteria were once a powerful technique by which many of the early antibiotics were found. However, when all the compounds that were easiest to be found this way and cultivate in a laboratory were identified, innovations largely dried up.

Dr. Lewis and his colleague at Northeastern, Dr. Slava Epstein, revived soil mining approach by inventing the iChip. This device allows growing in a lab bacteria that were impossible to cultivate by previous techniques. In this new approach, soil samples are placed between the iChip membranes and the device is buried back in the ground where bacteria can get nutrients from the soil in a natural way. Once colonies grow within the iChip, they are transferred back to the lab for discovering antibiotics.

Overall, about 50 000 strains of uncultured bacteria have been grown using the iChip and 25 new promising antibiotic compounds identified, including teixobactin. The new invention has a potential to solve the biggest issue of antibiotics research - the lack of drug candidates. Systems like the iChip enable exploration of large numbers of compounds with promising antibacterial properties which is the key to fighting the resistance phenomenon.

Northeastern University licensed the patent on the iChip technology and any compounds produced to an early-stage biotech company NovoBiotic Pharmaceuticals (Cambridge, MA), founded in 2003 by Northeastern University, Kim Lewis and Slava Epstein.

In order for teixobactin to become a drug treatment, several versions of the antibiotic must be produced via chemical synthesis in the process of drug development. In 2016 a group of researchers at the University of Lincoln, UK, have pioneered synthesis of its derivatives.

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As a concluding note, several major things happened within the antibiotics area over the last 5 years giving hope for the safer future without “superbugs”. First, the GAIN Act created the grounds for accelerating research and investment in the area of antibacterials discovery. Next, a number of antibiotics startups emerged on the wave of new incentives from government offering new therapies or empowering the existing antibiotics. It should be noted that new computational technologies mature, such as machine learning and artificial intelligence, and new promising interdisciplinary startups emerge to use them in facilitating drug discovery, including antibiotics research.

And finally, the recent breakthrough in bacterial cultivation with the iChip and teixobactin development gave a new hope to overcome the antibiotics apocalypse.

In addition to the above, governments around the world must act to reinforce strict regulations regarding antibiotics overuse in medical facilities as well as uncontrolled application in agriculture as this is crucial for decreasing the rate of bacterial mutations and associated resistance development risks. In fact, this kind of regulatory activities is being done also by some startups, for example, Accurx which is tackling the problem of eliminating inappropriate use of antibiotics.