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Exploring New Ways to Get at Old Bacterial Targets to Combat Resistant Strains

Arsenal must include not just souped-up me toos but also some brand new compounds

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While novel antibiotics are critically needed, some researchers say that there aren't a whole lot of new bacterial targets to aim at. New antibiotics may mean enhancing old ones to evade bacterial resistance mechanisms.

An article published last year by *The New England Journal of Medicine* pointed out, however, that superbugs are emerging faster than drugs to combat them can be developed. Both resistance mechanisms and rapidly moving genetic elements help bacteria stay ahead of the treatment curve, according to the researchers. Some of the regulatory constraints and finaning activites related to antibiotic development were discussed in our story "To Battle Super-Bugs, Antibiotic R&D Needs to Be Re-Incentivized."

GlaxoSmithKline's David Payne, Ph.D., vp, antibacterial discovery performance unit, told GEN, "To feel confident that we can tackle anything that bacteria can throw at us, we need fundamentally novel compounds." He said it was naive to think that resistance would not eventually develop to a new version of an old antibiotic.

The last completely novel antibiotic to emerge, Zyvox (linezolid), the founding oxazolidinone compound, was approved by the FDA in 2000 for treating vancomycin-resistant *enterococci* (VRE) and MRSA. One year after linezolid's approval, though, a paper was published in *The Lancet* about three patients with VRE who developed resistance to the new drug after a long period of treatment. Subsequently, other reports of resistance continued to appear in scientific literature.

Improving on Current Antibiotics

In 2006, Dirk Bumann, Ph.D., of the Hannover Medical School and associate at the Max Planck Institute for Infection Biology, reported an analysis of all possible pathways potentially available for known or new antibiotic intervention against *Salmonella*. While potential new targets could be defined, they were in known pathways already targeted for antibiotic therapy, they concluded.

"It is also now obvious that increasingly ineffective antibiotics ought to be replaced by similar but not identical active principles," Dr. Bumann's team stated. Their findings support the technique of tweaking existing antibiotics to make potential improvements in potency, increase efficacy range, and optimize other characteristics that might make them more tolerable, easily deliverable, and allow more convenient dosing.

The latest FDA approval, which came in 2010, was for Forest Laboratories' first-in-class fifth-generation cephalosporin Teflaro as a treatment for community-acquired bacterial pneumonia (CABP) and acute bacterial skin and skin structure infections (ABSSSIs) including MRSA.

Cephalosporins target the bacterial cell wall. Analysts estimate that the antibiotic could generate revenues of $361 million by 2014. Research has suggested that the antibiotic doesn't have a high propensity to develop a resistance.

In late-stage development are two compounds from Rib-X Pharmaceuticals' discovery platform. By leveraging the crystallographic structures of the ribosome, the company has reportedly been able to identify the atomic locations of resistance modifications and to produce multiple series of structurally distinct compounds effective against a wide range of pathogens.

Rib-X' delafloxacin is a fluoroquinolone antibiotic in Phase II for ABSSSIs including MRSA. Fluoroquinolones kill bacteria by blocking the activity of an enzyme required for DNA replication, DNA gyrase. The firm also has a souped-up oxazolidinone called radezolid, which is in Phase II CABP and uncomplicated SSSI trials.

Finding Entirely New Drugs

Dr. Payne said that GlaxoSmithKline recognized that antibiotic development required the "great science going on outside of GSK" as well as its internal programs. "We wanted to work with other companies and spread our scientific footprint in what we did in antibacterials to explore things that hadn't been explored before.

"We had an opportunity in 2009 to rewrite our strategy and formed autonomous small discovery units including one focused on antibacterials," Dr. Payne said. The benefit of that strategy, he told GEN, was a flexible, imaginative approach based on unexpected mechanisms that were not necessarily predictable with conventional drug development approaches.

As a result of actively collaborating with other companies and forming an in-house basic research department, GSK has two novel antibiotic candidates: GSK2251052, a protein synthesis inhibitor, and an inhibitor of bacterial peptide deformylase.

GSK2251052 originated from a discovery alliance with Anacor Pharmaceuticals and has completed Phase I trials. It is a boron-containing small molecule that blocks protein synthesis by inhibiting aminoacyl-tRNA synthesis in Gram-negative bacteria. The agent binds to the editing domain of a specific tRNA molecule, interfering with addition of the amino acid leucine and disrupting the appropriate sequence of amino acids, which eventually foils protein synthesis.

"No other known antibiotics work via inhibiting leucyl tRNA synthetase," Dr. Payne pointed out. The marketed topical antibiotic Mupirocin targets isoleucyl tRNA synthase. "Bacteria in the clinic are totally naive to this mechanism and don't have a resistance mechanism around it."

Another approach, gained by GSK through a 2008 alliance with Mpex Pharmaceuticals, explores inhibitors of bacterial efflux pumps. These pumps, intrinsic defense mechanisms in Gram-negative bacteria, expel toxins including antibiotics before they can reach their targets and kill the bacteria.

Higher intracellular antibiotic concentrations achieved through efflux pump inhibition could potentially increase the potency and pharmacological barrier against other drug resistance mechanisms. This may help maintain or even enhance the potency of otherwise effective antibiotics.

Dr. Payne echoed a view shared by drug developers that “we have to make sure that what we have done is sustainable, through developing a flow of diverse antibacterials. Just one new antibacterial today won’t solve the problem. What’s happened recently is that companies have withdrawn from the area so there’s a big gap in the pipeline, and we need to ensure it won’t happen again.”

Some novel compounds are emerging from newer players. Polymedix Biopharmaceuticals is developing antibacterials based on naturally occurring defensins, peptide molecules that have evolved in eukaryotes to protect them against bacterial infections.

PolyMedix founder, president, and CEO Nicholas Landekic explained to GEN that although peptides mimicking defensins have potential as antibiotics, their size, stability, tissue distribution, and toxicity limit their use as systemic drugs, making them most useful as topical agents.

PolyMedix got around this, he says, by designing and developing small synthetic organic compounds that mimic the defensins’ key molecular feature, the amphiphilic helix found in the natural molecules. The compound design exploits the inherent differences in charge and lipid composition between bacterial and eukaryotic cell membranes and affect only bacterial membranes. “The only thing that’s relevant for activity is a very specific arrangement of charged and hydrophobic groups,” Landekic pointed out.

Unlike conventional antibiotics with biochemical targets, Landekic added, these molecules act to kill bacteria by physically disrupting bacterial cell membranes. “Just like the natural host defense proteins, as soon as they come in contact with the bacterial membrane, our drugs form a pore in the membrane. Water then enters the membrane, causing it to swell, which disrupts the membrane’s inner structure. This destabilization results in membrane destruction.”

Landekic reported that the company has completed three Phase I studies in a total of 123 subjects with its lead compound, PMX-30063. Last September, a Phase II study in ABSSI for all drug-sensitive and drug-resistant hospital-based Staph infections began. “We expect to have final results by the end of the year for the full 200 patients, with an interim analysis planned after the first 80 patients have completed.”

While acknowledging the financial, regulatory, and research hurdles that have contributed to the dearth of new antibiotics, the Infectious Disease Society of America (IDSA) said this April that “the time has come for a global commitment to develop new antibacterial drugs.” In its paper entitled “Bad Bugs, No Drugs,” IDSA proposed its 10 x ’20 initiative, citing measures required to create 10 novel antibiotics by 2020.

The society called for global stakeholders to capitalize on each other's strengths to create a long-term, sustainable R&D infrastructure model that provides incentives for both antibacterial drugs and related diagnostic research enterprises.

Large companies like GSK, with a historical commitment to and deep knowledge of antibiotic development, that stay in the game can help realize the goal of the 10 x '20 initiative. So can smaller, highly innovative and strategically nimble companies with unique discovery platforms with sufficient support mechanisms in place to do it on their own.