Rediscovering antibiotics

By Chris Cain, Senior Writer

The implementation of the Generating Antibiotic Incentives Now Act and other recent efforts to speed antibiotic development will only be successful if they encourage new chemical approaches that address the dearth of new chemical classes in the antibiotics pipeline. Antibiotic developers contacted by *SciBX* said solving bacteria-specific challenges including rapidly emerging resistance and highly active drug export will be addressed only by investing in new structure-guided synthesis and screening programs.

Increased regulatory scrutiny by the FDA and a lack of clear financial motivation have taken their toll on the development of new antibiotics, with a trend of decreasing approvals over the past 30 years¹ (see Figure 1, “Antibiotic approvals over the last three decades in five-year increments”).

Moreover, just two new classes of broad-spectrum antibiotics have been approved in the last 40 years—the oxazolidinone Zyvox linezolid from **Pfizer Inc.** and the lipopeptide Cubicin daptomycin from **Cubist Pharmaceuticals Inc.**—both of which are only effective against Gram-positive bacteria. And reports of emerging multidrug-resistant Gram-negative bacteria, such as *Acinetobacter*, have stoked further concerns that there is not a robust pipeline of drugs to deal with the multiplicity of threats posed by an overall highly diverse and variable spectrum of pathogenic bacteria.

Jeffrey Stein, president and CEO of **Trius Therapeutics Inc.**, told *SciBX* that when it comes to antibiotic development, it has been a lack of financial incentives, and not scientific hurdles, that has stymied work. “The biggest challenge is not technical, it is financial, and that is because there is very little investment or interest in the early stage research required to come up with a clinical compound.”

To encourage companies to invest in antibiotics, the U.S. Congress passed the Generating Antibiotic Incentives Now (GAIN) Act, which took effect Oct. 1 as part of the FDA Safety and Innovation Act, which reauthorized prescription drug user fees. The law provides automatic priority review and an additional five to seven years of market exclusivity for some qualified infectious disease products (QIDPs).²

Members of Congress and biotech executives discussed how the legislation could aid antibiotic development on “*BioCentury This Week*”

earlier this month. FDA officials also discussed the agency’s Antibacterial Drug Development Task Force on a second “*BioCentury This Week*” program devoted to the topic.

Although the impact of the GAIN Act will take time to measure, several biopharma executives said it represents a sea change in attitudes toward antibiotic development.

Mark Leuchtenberger, president and CEO of **Rib-X Pharmaceuticals Inc.**, told *SciBX*, “The overall environment has turned from its nadir in the late 2000s, when four drugs went in front of FDA and only one came out. With initiatives in Europe and support from BARDA, there is now a much more propitious environment than there has been since the late ‘90s.”

The **Biomedical Advanced Research and Development Authority** (BARDA) is a U.S. Department of Health and Human Services program that prepares for potential public health emergencies in part by funding the development and purchase of drugs and vaccines.

In September, Rib-X’s lead compound, delafloxacin, was granted the first publically announced QIDP designation. The company plans to begin Phase III testing of the fluoroquinolone for acute bacterial skin and skin structure infections (ABSSSI) by the end of 2Q13.

John Rex, VP and head of infection and global medicines development at **AstraZeneca plc**, agreed with Leuchtenberger. “The whole tone of the conversation has gone from ‘no’ to ‘go,’” he said in an interview this month with *BioCentury*.²

Indeed, the EU’s **Innovative Medicines Initiative** (IMI) recently announced a €223.7 million (\$281.6 million) effort called New Drugs for Bad Bugs (ND4BB) to fund the clinical development of new antibiotics and create a consortium dedicated to basic research into Gram-negative pathogens.³

Until these efforts were proposed and implemented over the past year, “the incentives weren’t there from an early stage investor perspective,” said Ankit Mahadevia, a principal in the life sciences group at **Atlas Venture**. “Now we see the evolution of the landscape to be a lot like how the orphan drug landscape evolved several years ago. If there is pricing support for premium-priced antibiotics, there is a reasonable investment thesis around investing early, and as time goes on pharma will come back into the fold.”

The challenge now is to channel the optimism into new chemical classes of broad-spectrum antibiotics. The existing **clinical pipeline** is sorely lacking novelty, with no new classes of compounds in Phase III testing and only two in Phase II development.

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Trius Therapeutics Inc.**

Structural challenges

Companies leading the charge to develop new classes of antibiotics told *SciBX* that reliance on past approaches is not enough to fill the pipeline. Instead, recent structural and chemical advances must guide the discovery of the next generation of antibiotics.

Rib-X CSO Erin Duffy said the low rate of new antibiotic development is caused in part by not using the right kind of starting chemical matter in

Figure 1. Antibiotic approvals over the last three decades in five-year increments. In 1983–1987 the FDA approved 16 new systemic antibiotics, but since that time antibiotic approvals have been on the decline. Since 2008, only two systemic antibiotics have been approved. Vibativ telavancin from **Theravance Inc.** was approved in 2009 to treat acute bacterial skin and skin structure infections (ABSSSI), and Teflaro ceftaroline from **Forest Laboratories Inc.** was approved in 2010 to treat community-acquired bacterial pneumonia (CABP) and ABSSSI. (Figure based on Figure 1 in ref. 1.)

Source: Spellberg et al.; BCIQ: BioCentury Online Intelligence

enzymatic or cell-based screens. “The approach of saying, ‘I want to hit target X; I’ll screen until I get something’ didn’t work well because corporate libraries aren’t full of antibiotic-like compounds,” she said.

Stein agreed. “High throughput screening against large libraries has been largely ineffective. Most existing libraries and medicinal chemists who try to design new compounds create very lipophilic compounds. This means the solubility is very poor, and they do not cross bacterial membranes very well,” he said.

“The other truth is that people are pretty risk adverse. Everyone loves the idea of a novel scaffold, but they also hate the idea because they aren’t going to know what they get,” Duffy added.

Both Trius and Rib-X are taking a structure-based approach to design new antibiotics.

Rib-X is focused on antibiotics targeting the ribosome. The company has two new antibacterial programs in preclinical development, one of which is partnered with **Sanofi**.

Trius is developing new antibiotics against a range of bacterial targets including topoisomerase IV, DNA gyrase and the bacterial cell-wall enzyme UDP-N-acetylenolpyruvylglucosamine reductase (murB).

Stein said that innovation in the space is mostly coming from within biotech. “The truly novel antibacterials are being developed in small companies. Academic labs don’t have the funding to do this, and in large companies, those few that are doing antibacterial research are working on the next-generation cephalosporins or carbapenems. There is a limitation to how many generations you can make.”

However, Manos Perros, head of AstraZeneca’s Infection Innovative Medicines Unit (iMed), pointed out that his group also is investing in new chemical approaches. “My sense is there have been developments in the last three to four years that we can take advantage of, advances

in chemistry for one, as illustrated by our collaboration with the Broad Institute, where we can generate chemical starting points that look more like natural-product antibiotics, and thus we can start programs from a better place,” he said.

Last September, the pharma partnered with the **Broad Institute of MIT and Harvard** to screen a library of 100,000 compounds made by diversity-oriented synthesis, a process that generates molecular structures not contained in standard compound collections.

Cempra Inc. founder, president and CEO Prabhavathi Fernandes said it is important that new synthetic compounds interact with multiple sites on a target, as is the case for many naturally derived antibiotics. “When compounds inhibit a single site you get mutations and resistance develops. That is why natural products have been so popular—they bind multiple sites, and if bacteria mutate each site they either die or they are too sick to grow.”

Tetraphase Pharmaceuticals Inc. SVP of biology Joyce Sutcliffe agreed and emphasized that there is still room for new natural product-inspired antibiotics to overcome existing resistance mechanisms. “Knowing what the devil is often gives you an advantage,” she said.

Tetraphase is using its synthetic chemistry platform to develop new derivatives of tetracycline, a broad-spectrum polyketide antibiotic with activity against Gram-positive and Gram-negative bacteria. The company’s lead program, Eravacycline, has completed Phase II testing in community-acquired complicated intra-abdominal infections (cIAIs).

Both Sutcliffe and Fernandes pointed to the suspension earlier this year of clinical trials of GSK2251052, a bacterial leucyl-tRNA synthetase (lars; leurs) inhibitor from **GlaxoSmithKline plc** and **Anacor Pharmaceuticals Inc.**, as an example of how resistance can derail an antibiotic program focused on a single new target.

GSK returned rights to the compound to Anacor last month after resistance developed in a Phase IIb trial to treat urinary tract infection (UTI).

GSK still has two new broad-spectrum agents in the clinic. GSK1322322, a bacterial peptide deformylase (pdf) inhibitor, has completed Phase II testing and will enter Phase III trials as part of IMI’s ND4BB program. GSK2140944, a new bacterial topoisomerase IIA inhibitor, is in Phase I development.⁴

Cempra’s lead program is solithromycin, a fluoroketolide antibiotic that interacts with multiple sites on bacterial 23S rRNA. The compound is slated to begin Phase III testing to treat community-acquired bacterial pneumonia (CABP) Q412.

Gram negativity

The need for new chemical matter is particularly urgent for Gram-negative bacterial infections, which present unique challenges to the development of new drug classes.

“In terms of getting to a Gram-negative [bacteria] there are a lot more things at play. They have two membranes—and the outer membrane is pretty impermeable. If you can get through that and on your way to a molecular target, then you have to be able to test efflux, which is a problem in Gram positives but is really an issue in Gram negatives, which have 40 different efflux pumps. You have to figure out how not to be a substrate for that,” said Duffy.

To better understand these efflux pumps, ND4BB is spending €24 million (\$30 million) on new *in vitro* assays to study penetration

and efflux in multidrug-resistant Gram-negative bacteria, on bacterial porin structure and function research, on studies of nutrient uptake systems to identify new points of entry for antibiotics and on genetic screens to identify previously unknown targets that could improve drug penetration or reduce efflux.

“This is a place where the academic community could put their muscle to work,” said Sutcliffe.

AstraZeneca, **Basilea Pharmaceutica AG**, GSK, the Janssen R&D unit of **Johnson & Johnson** and Sanofi are participating in the effort.

Despite the challenges, Mahadevia said he was most interested in programs focused on Gram-negative bacteria. “Generally, I think Gram positives are well served by the pipeline and existing products. Gram negatives are where we are looking, pan-Gram-negative agents, but also targeting specific bugs such as *Pseudomonas*.”

Cempra’s Fernandes said it is important to keep historical perspective and not focus too narrowly on Gram-negative bacteria. “The unfortunate thing is we don’t know where the next bad bug is going to come from. Let’s say it is *Acinetobacter* now, but tomorrow it could be β -*Streptococcus*. We will need drugs against every major class of pathogens, and we cannot focus only on Gram negatives. Ten years ago all the focus was on staph, and no one looked at Gram negatives. Now it is all on Gram negatives.”

Future gazing

The development of rapid diagnostic tests to guide the clinical use of antibiotics also is a key next step to encourage antibiotic development. Identifying the causative agent of an infection is still a slow process relative to the lifetime of the infection; thus, antibiotic efficacy and approval rates would benefit from such improved detection methodologies.

Fernandes said designing a drug that treats a specific indication, rather than a specific pathogen, adds to the development challenge facing antibiotics. “When you talk about an infection, it’s not one disease. Let’s take pneumonia for example. There are five, six, seven bacteria that could cause the disease, and you have to treat all five bacteria with the same drug. There are many different targets there that you have to kill,” she said.

Cempra is collaborating with **Curetis AG** to use Curetis’ rapid diagnosis platform to collect data in Cempra’s Phase III CABP trial of solithromycin.

Rib-X’s Leuchtenberger also said that molecular diagnostics are promising but development is difficult. “All the key opinion leaders have said an accurate diagnostic is just around the corner for years, and it’s not there yet.”

AstraZeneca’s Perros agreed that the development of diagnostics for infectious diseases is an area in which more work is needed. “The way we treat disease today is empirical—every hour that passes reduces a patient’s chance for survival if you use the wrong antibiotics, so if you are in doubt

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—Ankit Mahadevia, Atlas Venture

you use the one with the broadest coverage and with activity against resistant infections. If you have a diagnostic that could easily tell you whether the patient needs the new drug, it would achieve several things in one—you would not treat patients with a new drug you don’t need and unnecessarily drive up treatment cost, and you would avoid promoting unnecessary development of resistance

to our latest treatments,” he said.

Perros said AstraZeneca is working in this area but has not disclosed specific antibacterial diagnostic partnerships.

Stein said molecular diagnostics could be particularly important for late-stage development. “It would be meaningful in a Phase III trial. For example, for a Gram-positive spectrum drug such as tedizolid, if it’s a lung study where Gram-negative or Gram-positive [bacteria] could be involved, it’s going to be important to prescreen prior to enrollment,” he said.

Trius’ tedizolid is in Phase III development for ABSSSI.

Sutcliffe agreed that for certain indications, such as CABP, a diagnostic could help reduce trial size and cost. However, she pointed out that it can be difficult to develop a specific antibacterial diagnostic to pinpoint the cause of an infection. “This is much harder than the diagnostics for antivirals because there aren’t usually intrinsic viruses running around in your blood stream. In the intestinal tract there are thousands of species of bacteria; if you take a sample there how will you know for sure which one is the causative pathogen?”

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COMPANIES AND INSTITUTIONS MENTIONED

Anacor Pharmaceuticals Inc. (NASDAQ:ANAC), Palo Alto, Calif.

AstraZeneca plc (LSE:AZN; NYSE:AZN), London, U.K.

Atlas Venture, Cambridge, Mass.

Basilea Pharmaceutica AG (SIX:BSLN), Basel, Switzerland

Biomedical Advanced Research and Development Authority, Washington, D.C.

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