

Mood at 2011 ICAAC: Renewed Optimism over Antimicrobial Prospects



"We go through peaks and valleys; this year, we have more optimism," says Karen Bush of Indiana University in Bloomington, referring to early stage antimicrobial agents being developed. She spoke during the poster summary session, "Early New Antimicrobial Agents," which she coconvened, part of the Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), held in Chicago, Ill., last September. This optimism extends to novel approaches to identifying antimicrobial drug candidates, she says. Although these newer agents are not yet being tested clinically, several are likely to progress toward clinical trials soon, she and other experts are saying.

These novel antimicrobials target a range of bacterial pathogens and reflect varied strategies for exploiting microbial vulnerabilities. For instance, PMX30063, a nonpeptide agent, mimics host-defense proteins and is rapidly bactericidal against staphylococcal infections, with broad activity against many drug-resistant isolates of such bacteria, according to Richard Scott of PolyMedix in Radnor, Pa. It is also active against *Bacillus anthracis*, he says. Several other compounds in this chemical family are active against fungal pathogens and malarial parasites.

Meanwhile, the tetrahydronaphthyridine spirocyclic pyrimidinetriones are "DNA gyrase inhibitors that are different from ciprofloxacin, with a different mode of action from fluoroquinolones," says Peter Doig of AstraZeneca R&D in Waltham, Mass. Some members of this class are not only active in vitro against both gram-positive and -negative bacterial pathogens, including *Escherichia coli*, but also prove active when tested in animals carrying such infections. Resistance rates are "low," and there is no cross-resistance with fluoroquinolones, he adds.

The bis-amidine antibacterials belong to yet another novel class of antibacterial agents, avoiding resistance by blocking efflux pumps in gram-negative bacterial pathogens, according to Michelle Butler of Microbiotix of Worcester, Mass. For example, MBX1162 from this class is rapidly bactericidal against *Staphylococcus aureus*, she says. Some of the bis-amidines can prevent pathogens from forming biofilms, but are not so active once those biofilms form.

RX-04 belongs to still another novel group of antibacterial agents that act by binding and blocking the activity of the large subunits of bacterial ribosomes, according to Erin Duffy of Rib-X Pharmaceuticals in New Haven, Conn. Although other established antibacterial agents target ribosomes, the binding site and action for RX-04 and others in this class are different, she points out. These and other molecules in the class offer "broad in vitro coverage" of bacterial pathogens, with strong activity against gram-negative and some activity against gram-positive bacteria. Although "efflux is an issue," she and her collaborators are tinkering with these molecules—including by examining 162 "virtual compounds"—to determine whether they can reduce efflux while retaining their ribosomal-binding and protein synthesis-inhibitory properties.

Some of the newer compounds being investigated are newer versions of established anti-infectives. For example, analogs of clofazimine, a drug identified for treating leprosy, show activity against *Mycobacterium tuberculosis*, the pathogen responsible for causing tuberculosis, according to Anna Upton of the Global Alliance for TB Drug Development in New York, N.Y.

Separately, several newly developed cyclic amidrazone or amidoxime derivatives of oxazolidinone display activity against linezolid-resistant gram-positive pathogens, according to Yong-Zu Kim of LegoChem Biosciences in Daejeon, South Korea. With linezolid still the only oxazolidinone approved for human use, he says, "we are continuing to optimize our lead compound and to support further development for use against gram-positive pathogens."

Meanwhile, FSI-1686 is one in a series of novel β -methylcarbapenem candidate antibiotics with good activity against gram-negative bacterial pathogens, according to Woo-Baeg Choi of FOB Synthesis in Kennesaw, Ga. Although FSI-1686 shows low activity against gram-positive pathogens, it has "good activity" against several notoriously difficult gram-negative bacterial

pathogens, such as *Acinetobacter baumannii* and *Pseudomonas aeruginosa*, he says.

Another promising development, described during other sessions at ICAAC, revolves around new β -lactamase inhibitors, agents that could help to overcome the activities of several different kinds of β -lactamases. β -lactamases render many β -lactam antibiotics ineffective, particularly against gram-negative bacterial pathogens, according to David Shlaes of Anti-Infectives Consulting in Stonington, Conn., who spoke during the ICCAC symposium, "New Antimicrobial Agents: What Every Clinician Should Know." Several such inhibitors are bicyclo-diaza-octanes, and two different members of this class are advancing in clinical trials deploying them in combination with one of several β -lactam antibiotics. "These are exciting times, and there's new hope," he says, easing a gloominess for which he is better known in his blog devoted to antibacterial developments.

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