strategy, according to Evans. Although dsRNA treatments are very effective at first, activity against Nosema drops sharply after two to three weeks, he says. He speculates that killing fails when some regulatory feedback loop kicks in within Nosema. Alternatively, if activity is restricted to the gut—the bees are fed the dsRNA molecules—rather than becoming systemic, control might wear off when the parasite infection ranges beyond the gut, Evans says. “We are starting to look at whether the effect can be transferred to other parts of the bee.”

“It appears likely that our major bee health problems have to do with coinfection of bees by multiple parasites, notably viruses and Nosema,” says Randy Oliver, an independent expert who runs the website ScientificBeekeeping.com and who was a principal investigator in a field trial testing RNA interference against bee viruses.

Bee colony collapse disorder threatens the sustainability of global agriculture because honeybees pollinate many crops. If this approach holds up, it could benefit farmers throughout much of the world, particularly in countries where beekeepers cannot use fumagillin, the sole treatment against the Nosema parasite, without having a prescription from a veterinarian, according to Oliver. “RNAi should not have that restriction,” he says.

However, this research on dsRNA goes well beyond colony collapse disorder. “If delivery mechanisms can be used successfully, many microsporidian pathogens of veterinary and human significance may become targets for nontoxic control—a highly desirable therapeutic utility for immunocompromised individuals,” Evans says.

Using dsRNA to interfere with Nosema opens the way to extensive functional analysis of microsporidian genes, says Emily Troemel of the University of California, San Diego. Microsporidia are obligate intracellular parasites with greatly reduced genomes—1/5 to 1/10 the size of typical fungi—and simpler cellular components, Evans says. For example, all that is left of the mitochondria is something called a “mitosome,” which contains only about 20 proteins, in contrast with roughly 1,000 in the yeast mitochondrion.

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At 50th ICAAC, More Candidates Coming from Novel Antimicrobial Classes

The candidate antimicrobial agents that drug developers brought forward during the 50th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) come largely from new molecular classes and include agents that just might prove effective against gram-negative bacterial pathogens that are carrying resistance to plenty of otherwise useful antibiotics. “There’s a future for some new antibiotics and new classes of them,” says Karen Bush of Indiana University in Bloomington, a co-convenor of the ICAAC poster summary session, “All New Antimicrobial Agents,” in Boston, Mass., last September. “We’re not there yet, but there’s hope.” Novel peptides, agents that block fatty acid synthesis or the early stages of protein synthesis, novel versions of tetracycline, and agents that block β-lactamase but do not themselves have antibacterial activity were among the candidates deemed worthy of special attention.

One of those new compounds, designated AN3365 (but now also bearing a GSK designation), is a boron-containing small molecule that blocks protein synthesis by inhibiting aminoacyl tRNA synthesis in gram-negative bacteria, says Dickon Alley of Glaxo-
SmithKline (GSK) in Collegeville, Pa. More specifically, the agent binds to the editing domain of a particular species of tRNA molecule, interfering with addition of the amino acid leucine. That derangement allows loading of other amino acids, in turn disrupting protein synthesis and poisoning bacterial cells. The agent has “fantastic activity” in vivo against a range of gram-negative pathogens, including those with resistance to a range of other antibiotics, he says. In phase I clinical studies, it appears to be “safe and well tolerated.” This boron-containing antimicrobial agent is “the first truly novel compound against gram-negatives to get through phase I in a long time.”

Fluoroceycline and others in a series of synthetic antibiotics in the tetracycline family belong to another class of novel inhibitors of protein synthesis with activity against a range of gram-positive and gram-negative pathogens, albeit not *Pseudomonas*, says Joyce Sutcliffe of Tetraphase Pharmaceuticals in Watertown, Mass. Like tetracycline, these compounds interfere with protein synthesis by binding to ribosomes. Some of the agents in this class show “good efficacy” in animals when administered either orally or intravenously. One of the lead compounds oddly has “higher oral availability in chimps than in dogs,” she says. “Ponder that.” Perhaps more importantly, these new agents appear not to be subject to several resistance mechanisms that render tetracycline ineffective against many important pathogens. Thus, they are “reinvigorating the tetracycline class,” and taking back the spectrum they once had,” she says. Phase I clinical and other data support the possibility that they can be used in once-daily oral doses.

The pleuromutilins, another new class of antimicrobial candidate drugs, also are active against both gram-positive and gram-negative pathogens, and also interfere with protein synthesis by binding to ribosomes, says Rodger Novak of Nabriva Therapeutics in Vienna, Austria. BC-3781, a lead compound in this class, is highly active against *Staphylococcus aureus*, including strains that are methicillin resistant (MRSA), he says. “We moved in four years from the test tube to clinical development.” In early clinical studies, he adds, the agent is “safe and well tolerated,” and in studies in animals it shows “good efficacy.” Although it overlaps with oxazolidinones, there is “no cross resistance with classic linezolid resistance,” he notes.

GSK1322322 is yet another new agent that interferes with protein synthesis—in this case, by targeting peptidyl deformylase, which removes formyl groups from new polypeptides as they are being formed in bacteria, according to Kelly Aubart of GSK. This new hydrazinopyrimidine agent has “good activity against gram-positive pathogens,” including those infecting the skin and soft tissue as well as the respiratory tract, she says. “It is potent in vivo and in vitro against a range of pathogens, including MRSA. Moreover it was safe and well tolerated in phase I studies.” The compound is undergoing phase II clinical testing of its activity in combating skin and soft tissue infections.

A new candidate drug in the fluoroquinolone (FQ) class, JNJ-Q2, is broadly active, including against MRSA isolates that are resistant to the widely used FQ antibiotic ciprofloxacin, and shows comparable activity to another member of this class, moxifloxacin, against gram-negative pathogens, according to Brian Morrow of Johnson & Johnson in Raritan, N.J. Unlike with ciprofloxacin, MRSA strains are slow to develop resistance to Q2 in vitro, and the new agent apparently does not up-regulate efflux pump mechanisms that render some bacteria effectively resistant to some antibiotics by expelling them, he says. Q2, which also is active against pathogens in biofilms, is being evaluated in phase II clinical trials involving patients with skin infections.

Some compounds are not antibacte-
rial on their own but enhance the activity of other established agents. For example, OligoG, an oligosaccharide derived from alginate polysaccharide, inhibits the growth of many gram-negative bacterial pathogens, including those with resistance to various kinds of antibiotics, according to Timothy Walsh of Cardiff University in Cardiff, United Kingdom, and his collaborators at Algipharma in Sanvika, Norway. “But it’s more complicated, and it exerts some effects even against gram-positive [pathogens].” OligoG seems to be synergistic with other antibiotics, including macrolides and β-lactams, and helps to disrupt biofilms. When used to treat patients with cystic fibrosis, it appears to reduce the minimal inhibitory concentrations (MICs) of other antibiotics, he says. It also is well tolerated in humans, and shows “no significant toxicities in dogs and rats.”

MK-7655, a class A and C β-lactamase inhibitor, another kind of agent without antibacterial of its own, was described by Mary Motyl of Merck & Co. in Rahway, N.J. Under development as an agent to help in treating β-lactamase-resistant gram-negative pathogens, MK-7655 restores the susceptibility of many such pathogens, including strains of *Pseudomonas aeruginosa*, to imipenem and other β-lactam antibiotics, she says. It also is effective against imipenem-resistant *Klebsiella pneumoniae*, lowering MICs and restoring susceptibility. Moreover, it seems to elude efflux pumps, suggesting that pathogens will not quickly overcome its antibiotic-restoring effects.

Finally in this set of promising new antimicrobial agents is the lone antifungal compound, E1210, with a novel mechanism of action and broad-spectrum activity, according to Frederick Duncanson of Eisai Inc. in Woodcliff Lake, N.J., speaking for his collaborators at the parent branch of Eisai in Tsukaba, Japan. This agent and others in its class inhibit acylation of glycosylphosphatidylinositol, which anchors glycoproteins into fungal cell walls. In some cases, its in vitro activity is greater than fluconazole, which is widely used clinically. Moreover, E1210 is not cross-resistant with fluconazole or otherazole antifungal agents, he says. Toxicity studies in rodents are “just starting,” but thus far there are “no unfavorable findings.”

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