FDA Approves Fidaxomicin for Treating C. difficile Diarrhea in Adults

Officials at the Food and Drug Administration (FDA) in May approved the antibiotic fidaxomicin for treating adults with diarrhea caused by Clostridium difficile. This macrolide antibiotic—originally called lipiarmycin to honor the leap-year day on which researchers in Italy discovered it—inhibits bacterial RNA polymerase by interfering with gene transcription. Its poor ability to be absorbed from the gastrointestinal (GI) tract helps to account for its effectiveness against C. difficile-associated diarrhea (CDAD). Typically, CDAD arises following antibiotic treatments, which can disrupt the microbial balance within the GI tract, enabling C. difficile to cause sometimes recurrent or persistent diarrhea that, in some cases, proves lethal, particularly among the elderly. CDAD appears to be on the rise in hospital and other institutional settings, and could affect 3 million patients in the United States per year, costing about $3 billion in the aggregate from extended stays and treatments. The drug, which is trademarked Dificid, was developed by Optimer Pharmaceuticals of San Diego, Calif.

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Infected Mosquitoes Hampers Parasites, as Might a Malaria Vaccine

Infected Anopheles gambiae mosquitoes with Wolbachia bacteria significantly lowers levels of the malaria parasite Plasmodium falciparum in those insects and thus interferes with their capacity to transmit malaria parasites to humans, according to Jason Rasgon at Johns Hopkins University in Baltimore, Md., and his collaborators. However, Wolbachia infect only somatic cells of their mosquito hosts. For this parasite-reducing approach to be practical or useful against malaria, Wolbachia somehow must also infect germ line cells to be transmitted to offspring. “We and others are trying to establish natural infections in Anopheles that can be vertically transmitted,” Rasgon says. “Transmission to offspring remains a hurdle.”

“This is the first time that anyone has shown that Wolbachia infections can reduce levels of the human malaria parasite in Anopheles,” he says. Whether this approach proves practical depends in part on learning how to transmit Wolbachia efficiently between generations of mosquitoes—and, ultimately, on combining this approach with others, including development and use of vaccines.

Although Wolbachia infect a broad range of insects, the bacteria do not associate naturally with Anopheles. However, after Rasgon and his colleagues inject Wolbachia strains wMelPop and wAlbB into the thoraxes of female mosquitoes, both bacterial strains not only persist but also infect diverse tissues and organs, including the gut, abdomen, head, and fat body, but not the ovaries. Moreover, after the bacteria infect insect tissues, localized P. falciparum oocyte development is reduced by 40 to 60%. Meanwhile, host immunity genes are down-regulated, enabling Wolbachia to persist for as long as the host mosquitoes remain alive. Details appear in the May 11, 2011 PLoS Pathogens [doi: 10.1371/journal.ppat.1002043].

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“Despite increases in plastic production, the best data available do not indicate measurable increases in plastic debris in the Atlantic,” says oceanographer Angelique E. White of Oregon State University. “It may be that the plastic degrades to particle sizes less than what can be captured by nets, but at what rate? Changes in the buoyancy of plastic may also occur during degradation or as a result of colonization by microbes/sessile organisms. This could lead to settling of plastic debris out of the surface ocean. . . . One additional removal term might be via microbial decomposition of the polymer residues—a question that remains largely unexplored from the perspective of the enzymatic diversity of oceanic flora.”

“Plastics will eventually biodegrade, even in the ocean, but the time it takes for this to happen remains a serious problem,” says Charles Moore of the Algalita Marine Research Foundation in Long Beach, Calif. “The accelerators can’t improve much on this persistence aspect, nor can enhanced suites of microbes that are better at eating plastic because competing, more easily assimilable nutrient sources are always present.”

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Plasmodium falciparum is the most dangerous of the parasites that cause malaria and results in over 1 million deaths annually. This apicomplexan parasite is capable of adapting to infect diverse tissues, localized P. falciparum oocyte development is reduced by 40 to 60%. This leads to decreased transmission of Plasmodium falciparum to offspring. However, Wolbachia infect only somatic cells of their mosquito hosts. For this parasite-reducing approach to be practical or useful against malaria, Wolbachia somehow must also infect germ line cells to be transmitted to offspring. “We and others are trying to establish natural infections in Anopheles that can be vertically transmitted,” Rasgon says. “Transmission to offspring remains a hurdle.”

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ically, *Metarhizium anisopliae* and *Beauveria bassiana*—suspended in synthetic oil, according to Tullu Bukhari of Wageningen University in Wageningen, the Netherlands, and collaborators. The oil protects the fungal spores and promotes their spread across bodies of water in which mosquito larvae hatch and mature. The oil-spool mixture killed 50% more larvae than did fungal spores alone when evaluated at a test site in Kenya. The mix does not harm other aquatic life. Details appeared online in the February 2011 *Parasites & Vectors.* [doi: 10.1186/1756–3305-4–23].

Yet another plan involves vaccinating humans to block the chain of parasite transmission, according to Nibhabh Kumar at Tulane University in New Orleans, Louisiana. He and his collaborators are evaluating an experimental vaccine that is aimed at generating antibodies in humans that will neutralize malarial parasites inside mosquitoes, he says. Individuals carrying the malaria parasite will not benefit directly from this “public health prevention approach,” whose goal is to lower “transmission . . . at the community level. When the mosquito bites another person, it cannot transmit parasites.” The linchpin of this experimental vaccine is Psf48/45, a protein that generates antibodies in mice and baboons; in turn, those antibodies reduce malaria parasite transmission by as much as 93%. He and his collaborators are developing a similar vaccine to block *P. vivax,* which together with *P. falciparum* “accounts for 90% of malaria infections worldwide,” he says.

**Carol Potera**
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**Quorum Sensing Inhibitors Enhance Antibiotics against Biofilms**

Combining quorum sensing (QS) inhibitors with antibiotic treatments greatly boosts their efficacy against biofilms containing the same bacterial pathogens that infect the lungs of cystic fibrosis (CF) patients, according to Tom Coenye of Ghent University in Ghent, Belgium, and his collaborators. “Overall the use of quorum sensing inhibitors drastically increased the effect of the antibiotic,” he says. However, although these combination treatments prove effective against in vitro and in experiments involving animals, they do not change antibiotic susceptibilities of the planktonic forms of the pathogens. Details appear in the June 2011 *Antimicrobial Agents and Chemotherapy* (55: 2655–2661).

Research by Michael Givskov and his collaborators, showing that QS contributes to the resistance of biofilms to antibiotics, “led us to investigate the combined use of these two classes of molecules,” Coenye says. He and his collaborators infected several kinds of animals, including *Caenorhabditis elegans* nematodes, *Galleria mellonella* greater waxmoth larvae, and mice with various biofilm-forming bacterial pathogens, including *Burkholderia cenocepacia,* *B. multivorans,* *Pseudomonas aeruginosa,* and *Staphylococcus aureus.* Although the results varied from one specific case to another, QS inhibitors combined with mixes of several antibiotics boosted survival of infected *G. mellonella* larvae and *C. elegans* compared with groups in which QS inhibitors were administered with only one type of antibiotic, according to the Belgian research group.

Moreover, even without antibiotics in the mix, QS inhibitors, which are involved in regulating virulence factors, proved beneficial for infected animals in some cases, according to Coenye. For example, QS regulates *B. cenocepacia* synthesis of a nematode-killing protein. Further, inhibiting QS interferes with the swarming motility of bacteria, possibly blocking their dissemination within the host during infections.

To determine whether mechanisms other than QS contribute to the synergy between QS inhibitors and antibiotics, the Belgian team tested a mutant of *P. aeruginosa* that cannot produce certain QS signaling molecules. “Compared to the wild type, this mutant was much more susceptible to tobrinomycin, which confirms the role of a functional [QS] system in resistance,” the researchers note. “In addition, while [baicalin

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**U.S. Ponders Changing Select Agents Policies; WHA Postpones Destroying Smallpox**

A top-level federal advisory group in June recommended paring the number of tier-1 agents, which are the most restricted biological select agents and toxins, to about one dozen items; strengthening current procedures for vetting researchers and setting other criteria to limit who will be permitted to study or work with such agents; and reevaluating physical and cyber security standards at institutions where such agents are studied. These recommendations from the Federal Experts Security Advisory Panel, which was established in mid-2010 and is chartered through 2014, are provided to the directors of the federal Select Agents Program, a group that sets rules and policy on such matters. For more information, see http://www.selectagents.gov. Separately, the World Health Assembly, the policy arm of the World Health Organization, last May reaffirmed the goal, but postponed destroying smallpox virus stocks being held in the United States and Russia. WHA will next review smallpox research and the disposition of smallpox virus stocks in 2014.