MINITOPIC

Shapes and Curves; Plus Revised View of Cell-Wall Growth

The shapes of microbial species are sometimes fanciful and can be important for their survival or may mask activities that are key to physiology. Recent examples include:

- *Helicosporidium*, a corkscrew-shaped intracellular parasite that feeds on juvenile insects, derived from algae but, unlike *Plasmodium*, the parasite responsible for malaria which also derived from algae, retained most of its genes except those explicitly needed for photosynthesis, according to Patrick Keeling of the University of British Columbia (BC) in Vancouver, B.C., Canada, and his collaborators. Details appeared 8 May 2014 in *PLoS Genetics* (doi:10.1371/journal.pgen.1004355).
- In gently moving water, the curvature of *Caulobacter crescentus* cells helps to point progeny swarmer cells toward the surface, where they go to attach to similar cells, enlarging the growing colony, according to Alexandre Persat and Zemer Gitai at Princeton University and their collaborators. Details appeared 8 May 2014 in *Nature Communications* (doi:10.1038/ncomms4824).
- The cell wall enzyme PBP2 and the bacterial actin homolog MreB are active on drastically different time scales, suggesting that cell wall growth in gram-negative bacteria depends on dynamic instead of stable complexes involving these and other proteins, according to K. C. Huang of Stanford University in Stanford, Calif., and his collaborators. Thus, for example, the cell wall keeps growing under osmotic stress but the new segments remain shriveled until conditions allow them to expand and take their rightful shape. Details appeared 12 May 2014 in the *Proceedings of the National Academy of Sciences* (doi:10.1073/pnas.1313826111).

WHO takes great pains not to embarrass individual countries for how well or poorly they "measure up," and this low-key approach ends up being a "core problem," Fineberg says. Although the idea of WHO helping in efforts to assess a country's capacity to deal with emerging infectious diseases "makes sense, national governments don't like it," Fukuda adds, noting that only about 20% of the countries have the appropriate capacity. "WHO is well-positioned to help with quality assessments, but we haven't found the right way to achieve the necessary political balance."

Another looming issue is how best to deal with the Convention on Biological Diversity (CBD), an international agreement from 1992 that was never intended to deal with public health issues. Nonetheless, some of its provisions bump into matters concerning IHR 2005, particularly when it comes to sharing of biological materials that, for example, might prove critical for the development of diagnostic tests and vaccines. "What can you do?" Fukuda asks. "This framework [the CBD] is seen as being 'over there,' having nothing to do with health, but we realize it does."

Jeffrey L. Fox is the Microbe *Current Topics and Features Editor.*

NEW IN ASM JOURNALS

Freely Diffusing Topical Antifungal Agent Fixes Infected Toenails

David C. Holzman

The candidate antifungal drug efinaconazole is proving effective against toenail infections. The drug diffuses relatively freely through nails and binds less strongly to keratin than do other topically applied antifungal drugs, leaving it free to fight the fungus, according to Keita Sugiura of Kaken Pharmaceutical of Kyoto, Japan, and his collaborators. "This study suggests that . . . low keratin affinity is needed for favorable penetration and retention of antifungal activity within the nail matrix," he says. Details appeared online 21 April 2014 and will be printed in the July 2014 *Antimicrobial Agents and Chemotherapy*.

Because topical antifungal drugs so often fail to cure this condition, physicians sometimes prescribe oral antifungal drugs such as terbinafine and itraconazole for some of their patients with stubborn cases of onychomycosis. However, Sugiura points out, this approach "is limited" because such drugs can damage the liver or may interact with other drugs that patients are taking. Although topically applied antifungal drugs such as ciclopirox and amorolfine have "a favorable safety profile," he adds, "their cure rates are considerably lower."

Sugiura and his collaborators tested human nails to find how well the drug diffuses through keratin-rich nails. Small 16 mm^2 squares from commercially available toenail material (who knew?) were mounted in Franz diffusion cells to measure how quickly several antifungal drugs pass through that material. Efinaconazole proved speediest, racing through the mounted nail squares within the first day, while ciclopirox took six days and amorolfine remained undetected, they report.

Of several drugs tested, only efinaconazole inhibited fungal growth under nails in vitro, according to Sugiura. He and his collaborators also tested the fungicidal activity of several topical antifungal products in a fluid keratin medium that is designed to "mimic the keratin-rich environment of the nail plate and nail bed." Without a solid matrix to block the drugs, efinaconazole proved slightly more potent at killing

Fungal infections of toenails are particularly difficult to treat, chiefly because it is difficult to get antifungals to penetrate the nail. A new topical antifungal, efinaconazole, shows good penetration into infected nails and may be a breakthrough for treating infections that previously could only be treated with orally administered drugs. (Image © iStockphoto/4kodiak.)

the fungus than did amorolfine and far more potent than ciclopirox, they note.

"Efinaconazole is the first topical drug that has shown efficacy for this persistent and common infection," says Boni Elewski of the University of Alabama, Birmingham, who last year led a pair of phase 3 clinical studies to evaluate this drug for treating onychomycosis, the formal name for chronic fungal infections of toenails. "I think this mechanism of action is indeed quite significant, contributing to the relatively high mycologic cure rate in treating onychomycosis," says Elewskii.

The typical fungi responsible for onychomycosis include *Trichophyton rubrum*, *T. mentagrophytes*, *Candida albicans*, and nondermatophyte molds. The condition affects about 8% of the U.S. population, mainly adults, particularly those who are 60 years of age or older. While more a cosmetic than a frank health issue, onychomycosis can prove painful as well as being an eyesore, and may interfere with work that entails standing, food handling, modeling, or other interactions and relationships, Elewski points out.

David C. Holzman is the Microbe *Journal Highlights Editor.*

RESEARCH ADVANCES

Promising Tuberculosis Drug also Targets Vastly Different Microbes

Carol Potera

A promising candidate drug for treating tuberculosis (TB), called SQ109 and undergoing phase 2 clinical trials, acts against *Mycobacterium tuberculosis* as well as other microbial pathogens and parasites via several different mechanisms, according to Eric Oldfield at the University of Illinois, Urbana-Champaign, and his collaborators. Not only SQ109, but also a series of analogues inhibit the growth of a range of microorganisms, acting at various molecular targets—leading to "very low rates of spontaneous drug resistance," they report. "There's an urgent need for new drugs that are resistance-resistant, and drugs that hit multiple targets will reduce resistance," Oldfield adds. Details appeared February 25, 2014 in the *Journal of Medicinal Chemistry* (doi:10.1021/jm500131s).

SQ109 is a 1,2-diamine that is related to ethambutol, a widely used drug that is bacteriostatic against *M. tuberculosis*, blocking cell-wall production. Sequella, Inc. in Rockville, Md., a company focused on TB, began developing SQ109 in 2000, then in partnership with researchers at the National Institutes of Health (NIH) in nearby Bethesda, Md. Several years ago, members of the NIH group and their collaborators reported that SQ109 "interferes with the assembly of mycolic acids into the cell wall core of *M. tuberculosis*." They also concluded that the primary bacterial target for the drug was MmpL3, "a transporter of trehalose monomycolate," an ingredient of the cell wall in *M. tuberculosis*.

That seeming clarity for how SQ109 and analogues like it work, however, proved to be less than complete. Other researcher groups reported that SQ109 acts against other microbial species, including *Helicobacter pylori* bacteria and *Candida albicans*, a yeast. Neither one of them produces the MmpL3 transporter or makes cell walls like those of *M. tuberculosis*. Those and other results suggest that there must be other cellular targets for SQ109 and its analogues.

Oldfield and his collaborators tested SQ109 and a series of analogues against a battery of five bacteria, including *M.*

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Synthetic Biology: Microbe Reaches First Base with Odd Nucleotides

An engineered version of *Escherichia coli* can grow normally while stably carrying unnatural nucleotide base pairs within a replicating plasmid, according to Floyd Romesberg of the Scripps Research Institute in La Jolla, Calif., and his collaborators. Triphosphate versions of those unnatural base pairs, designated d5SICS and dNaM, are brought into the *E. coli* bacterial cells via an algal transporter protein, and the DNA replication machinery of those cells "uses them to accurately replicate a plasmid," they report. The bacterial DNA repair apparatus leaves the altered plasmids alone, and the addition of the synthetic base pairs, which are not being translated into novel amino acids, does not appear to slow down the growth of the altered cells. Their next step in this research, Romesberg and his collaborators say, "will be to demonstrate the in-cell transcription of the new, expanded-alphabet DNA into the RNA that feeds the protein-making machinery of cells." Details appeared May 7, 2014 in *Nature* (doi: 10.1038/nature13314).