such criteria and, as an important bonus, has strengthened health delivery systems in dozens of developing countries—thus bringing the more ambitious goal of health equity a bit closer.

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Host-Targeted TB Therapies of Limited Efficacy So Far
Shannon Weiman
*Mycobacterium tuberculosis* (Mtb) is notoriously difficult to eradicate even with combinations of antibiotics, leading researchers to pursue alternate strategies, including one aimed at bolstering host defenses against this pathogen. “Our inability to effectively treat all infected individuals necessitates a deeper understanding of the host-pathogen interface to facilitate new approaches,” says Amy Barczak of the Ragon Institute and Massachusetts General Hospital in Boston, Mass. She was one of several experts who participated in the symposium “Aiming at Non-Conventional Approaches to TB Therapies,” held at the 2016 ASM Microbe Conference in Boston last June.

Mtb exploits innate immunity to its advantage, according to Jeffery Cox of the University of California, Berkeley. Inside host macrophage cells, the pathogen ejects its DNA from phagosomes into the cytosol, where it is misidentified as viral DNA, tricking the host cell into mounting misdirected antiviral responses that favor Mtb survival. Specifically, various immune modulators, including OasL1 (2′-5′-oligoadenylate synthase-like protein 1), which controls type-1 interferon (IFN) production, are degraded. “We suspect that this primarily antiviral pathway has been co-opted by bacterial pathogens, perhaps primarily to elicit type-1 IFNs,” he says, adding that blocking OasL1 ubiquitinylation might shift host immunity back toward antibacterial responses.

Mtb also exploits host cytokine signaling, further helping it survive within phagosomes, according to Priscille Brodin of the Institut Pasteur de Lille, France. She is investigating a mechanism by which phagocytosis of Mtb triggers cytokine signaling pathways that ultimately block phagosome acidification. Cancer drugs that target these pathways may thwart Mtb’s survival strategy, promoting phagosome maturation to kill internalized Mtb.

Meanwhile, although a cyclic-di-AMP-dependent cytosolic surveillance mechanism detects Mtb second messengers and activates antibacterial autophagy defenses, Mtb encodes a phosphodiesterase that degrades cyclic-di-AMP, allowing it to fly under the radar, according to William Bishai of Johns Hopkins University in Baltimore, Md. Phosphodiesterase inhibitors, including drugs widely used to treat erectile dysfunction, might give the upper hand back to the immune system, he points out.

Other drugs that promote autophagy defenses and benefit the host include the antidepressant fluoxetine and the cancer drug gefitinib, according to Barczak. “Fluoxetine induces autophagy and enhances production of tumor necrosis...
MINITOPIC
Mechanisms and Microbes: Resistances, Antimicrobials, and Prions

Recent developments involving mechanistic insights into microbially related molecules and processes include:

- A transferable (plasmid-borne) resistance gene for colistin, called mrc-1, was recently detected in in the United States in a patient whose urinary tract was infected with Escherichia coli, following detection of this gene in other pathogens outside this country, according to Patrick McGann at the Walter Reed Army Institute of Research in Silver Spring, Md., and his collaborators. Details appeared 26 May 2016 in Antimicrobial Agents and Chemotherapy (doi:10.1128/AAC.01103–16).
- In addition to blocking protein synthesis, streptomycin (specifically, the dihydro derivative) binds and modifies the MscL membrane channel pore of targeted bacterial cells, allowing materials to leak from them and this antibiotic to gain entry, according to Paul Blount, Junmei Wang, and their collaborators from University of Texas Southwestern Medical Center in Dallas. Details appeared June 9, 2016 in PLOS Biology (doi:10.1371/journal.pbio.1002473).
- New candidate drugs for treating malaria apparently stimulate sodium ions to enter the parasite that causes this disease, changing its outer membrane and leading it to divide before its genome replicates, according to Akhil Vaidya from Drexel University College of Medicine in Philadelphia, Pa., and collaborators. Details appeared May 26, 2016 in PLOS Pathogens (doi:10.1371/journal.ppat.1005647).
- Toxoplasma gondii parasites can directly disrupt the neurotransmitter glutamate in the brains of rodents such as mice, leading it to build up and disrupting the behavior of such animals, according to Emma H. Wilson of the University of California, Riverside, and her collaborators. Details appeared June 9, 2016 in PLOS Pathogens (doi:10.1371/journal.ppat.1005643).
- Prions kill neurons in vitro by causing their dendritic spines to retract, a prelude to the subsequent destruction of these cells of the central nervous system, according to David Harris from Boston University School of Medicine in Boston, Mass., and his collaborators. Details appeared May 26, 2016 in PLOS Pathogens (doi:10.1371/journal.ppat.1005623).