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BACTERIAL PATHOGENESIS

Editors: Tyrrell Conway, Professor and Head of Department of Microbiology and Molecular Genetics, Oklahoma State University; Paul S. Cohen, Professor of Cell and Molecular Biology, University of Rhode Island

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The Nature of Science

I wrote a letter to Microbe, published in the October 2010 issue, p. 412–413, that discussed the similar erroneous prejudices that scientists of the applied and research fields often hold for each other. With this letter I would like to discuss other perceptual anomalies scientists have grown to embrace. They relate to exactly what science is in the minds of scientists.

Science is far more than statistics, or more than what has exclusively been published in journals. The science a scientist is expected to employ also largely involves good value judgment and reasoning based on his or her personally accumulated knowledge.

Furthermore, just as pure statistics is not the whole of science, pure math will not replace creative conceptual reasoning by the human mind. I heard a theoretical physicist proclaim on a science talk show that any significant cosmological advancements in the science would only come from mathematics. The Einstein-borne era of conceptual advancement of our understanding of The Universe was over.

Along a similar vein, I tire of hearing of molecular biologists discovering microbial phenomena that I learned in my 1973–4 bacteriology courses. Back then the genome of E. coli had been mapped, microbiologists understood the value of bacteria to our health and the environment, the human microbiome was being studied, etc. The methods were slow, but sufficiently productive. The false assumptions relating to past knowledge that fuel some contemporary research show a lack of literature review, as well as educational background. New and adjunctal data should be introduced, but not premised with false “they used to believe” generalizations, and not as if the entire study is unique to science.

The U.S. Patent Office rejects patent applications for a variety of reasons, but the two most common are when an idea is “in the realm of the public,” or when the idea seems “obvious” to the examiner. Maybe these two criteria should also be used by journal editors before accepting a paper for publication.

I hope my comments do not seem too negative, because I still have great faith in science and in scientists, but I believe there are occasional drifts in science perception and application that need correcting.

Dennis R. Hill
Des Moines Water Works
Des Moines, Iowa
Global Action Plan on Antimicrobial Resistance

The 68th World Health Assembly (WHA) issued this plan for action on 26 May 2015

Aware that access to effective antimicrobial agents constitutes a prerequisite for most modern medicine; that hard-won gains in health and development, in particular those brought about through the health-related Millennium Development Goals, are put at risk by increasing resistance to antimicrobials; and that antimicrobial resistance threatens the sustainability of the public health response to many communicable diseases, including tuberculosis, malaria and HIV/AIDS;

Aware that the health and economic consequences of antimicrobial resistance constitute a heavy and growing burden on high-, middle-, and low-income countries, requiring urgent action at national, regional and global levels, particularly in view of the limited development of new antimicrobial agents;

Recognizing that the main impact of antimicrobial resistance is on human health, but that both the contributing factors and the consequences, including economic and others, go beyond health, and that there is a need for a coherent, comprehensive and integrated approach at global, regional and national levels, in a “One Health” approach and beyond, involving different actors and sectors such as human and veterinary medicine, agriculture, finance, environment and consumers;

Aware that the inappropriate use of antimicrobial medicines in all relevant sectors continues to be an urgent and widespread problem in high-, middle-, and low-income countries, with serious consequences for increasing antimicrobial resistance in a wide range of pathogens including bacteria, viruses and parasites;

Noting that despite sustained efforts over a number of decades by Member States, the Secretariat and partners, most developing countries are still facing a multitude of challenges in improving affordability and universal access to quality, safe and effective antimicrobial medicines and diagnostic tools;

Recognizing that, although substantial investments have already been made to tackle antimicrobial resistance, significantly more resources need to be mobilized to support effective action at national, regional and global levels, including through the provision of technical and financial assistance, particularly to low- and middle-income countries;

Reaffirming the critical importance of enhancing infection prevention and control, including good sanitation and hygiene, in both community and health care settings;

Recognizing the importance of immunization as one of the most cost-effective public health interventions, and that vaccines play an important role in reducing antimicrobial resistance;

Underlining the pressing need to develop new antimicrobial medicines as well as effective, rapid, and low-cost diagnostic tools, vaccines and other interventions, and recalling the Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property and resolution following up on the report of the Consultative Expert Working Group on Research and Development: Financing and Coordination, which address drug market failure;

Acknowledging the urgent need for a more coordinated and harmonized surveillance system to monitor antimicrobial resistance at national, regional, and global levels, including the need to develop internationally agreed standards for data collection and reporting across the human health, medical, veterinary and agricultural sectors;

Underscoring the need to improve awareness and understanding of antimicrobial resistance through effective public communication programs, education, and training as well as in the human health, veterinary and agricultural sectors,

ADOPTS the global action plan on antimicrobial resistance and URGES Member States:

- To implement the proposed actions for Member States in the global action plan on antimicrobial resistance, adapted to national priorities and specific contexts;
• To mobilize human and financial resources through domestic, bilateral and multilateral channels in order to implement plans and strategies in line with the global action plan on antimicrobial resistance;
• To have in place, by the 70th World Health Assembly, national action plans on antimicrobial resistance that are aligned with the global action plan on antimicrobial resistance and with standards and guidelines established by relevant intergovernmental bodies; and, where applicable, regional economic integration organizations.

INVITES international, regional, and national partners to implement the necessary actions in order to contribute to the accomplishment of the five objectives of the global action plan on antimicrobial resistance;

REQUESTS the Director-General:
• To implement the actions for the Secretariat in the global action plan on antimicrobial resistance;
• To ensure that all relevant parts of the Organization, at headquarters, regional and country levels, are actively engaged and coordinated in promoting work on containing antimicrobial resistance, including through the tracking of resource flows for research and development on antimicrobial resistance in the new global health research and development observatory;
• To strengthen the tripartite collaboration between the Food and Agriculture Organization (FAO), the World Organisation for Animal Health (OIE), and World Health Organization (WHO) for combating antimicrobial resistance in the spirit of the “One Health” approach;
• To work with the Strategic and Technical Advisory Group on antimicrobial resistance, Members States, FAO, and OIE, and other relevant partners to develop a framework for monitoring and evaluation in line with principle five of the global action plan on antimicrobial resistance;
• To develop and implement, in consultation with Member States1 and relevant partners, an integrated global program for surveillance of antimicrobial resistance across all sectors in line with the global action plan on antimicrobial resistance;
• To establish a network of WHO Collaborating Centers to support surveillance of antimicrobial resistance and quality assessment in each WHO region;
• To develop, in consultation with Member States and relevant partners, options for establishing a global development and stewardship framework to support the development, control, distribution, and appropriate use of new antimicrobial medicines, diagnostic tools, vaccines, and other interventions, while preserving existing antimicrobial medicines, and promoting affordable access to existing and new antimicrobial medicines and diagnostic tools, taking into account the needs of all countries, and in line with the global action plan on antimicrobial resistance, and to report to the 69th WHA;
• To work with the UN Secretary-General and bodies in the United Nations system to identify the best mechanism(s) to realize the investment needed to implement the global action plan on antimicrobial resistance, particularly with regard to the needs of developing countries;
• To elaborate, in consultation with the UN Secretary-General, options for the conduct of a high-level meeting in 2016, on the margins of the UN General Assembly, including potential deliverables, and to report to the 69th WHA through the 138th Executive Board; and, where applicable, regional economic integration organizations.
• To provide support and technical assistance to countries, with a specific focus on low- and middle-income countries;
• To set aside adequate resources for the Secretariat, in line with the Program budget 2016–2017 and the Twelfth General Programme of Work, 2014–2019 for implementing the global action plan on antimicrobial resistance;
• To submit biennial reports on progress achieved in implementing this resolution to the 70th, 72nd, and 74th WHA, and to produce an interim report to the 69th WHA.
ASM MEETING

Revisiting Natural Products, Seeking Antimicrobial Candidates

Shannon Weiman

Spices such as ginger and cinnamon as well as other natural products have potent antimicrobial activities against methicillin-resistant *Staphylococcus aureus* (MRSA), various strains of *Pseudomonas aeruginosa*, and other pathogens, including those that form biofilms, according to several researchers who presented findings during the 2015 ASM General Meeting, held in New Orleans, La., last May. If they prove safe and effective, these natural products or derivatives based on them could lead to new treatment strategies for infections caused by these clinically challenging bacterial strains, the researchers say.

The galacto-oligosaccharide raffinose is a constituent in ginger that inhibits biofilms formed by *P. aeruginosa*, according to Eunji Cha of Korea University. The compound acts by decreasing cyclic-di-GMP, an intracellular signaling molecule that controls the switch between planktonic and sessile (biofilm) lifestyles, she says. "New strategies for treatment focus on manipulating biofilm development without affecting bacterial growth." That sugar might be a useful ingredient in coatings to prevent biofilms from forming on medical devices, she notes.

Some natural remedies show surprising specificity, according to Rebecca Gabrilskas of Texas Tech University Health Sciences Center in Lubbock. A medieval remedy for eye infections—a mixture of garlic, oxgall (cow bile), wine, leek or onion, and copper salts—is active against MRSA but not other bacterial pathogens, including *P. aeruginosa*, vancomycin-resistant *Enterococcus faecalis*, or *Acinetobacter baumannii*, according to Gabrilskas and her collaborators at the University of Nottingham, United Kingdom.

"Efficacy only against the MRSA component of the polymicrobial population indicates specificity in the mechanism of action," Gabrilskas says. "The efficacy of Bald’s eyesalve on MRSA was comparable or better than that of the gold standard, the last-line antibiotic vancomycin." Directions for making this concoction were translated from a 9th-century Anglo-Saxon medical manuscript, "Bald’s Leechbook," enabling her and her collaborators to make and then test the concoction in the laboratory. Because none of the ingredients in the mixture was effective when tested on its own, she and her collaborators plan to determine the antimicrobial mechanism of the mixture, hoping also to identify key active compounds within it.

Some natural products have potentially useful antiviral rather than antibacterial activity, according to Milton Schiffenbaur of Touro College in New York, N.Y. For example, polyphenol extracts from *Camellia sinensis*, a shrub whose leaves and buds are used to make tea, has antibacterial and antiviral properties. Moreover, among extracts of cloves, citron pulp, dark chocolate, Spanish saffron, peppermint, onion, garlic, and cinnamon, only cinnamon extracts show activity against various bacteriophage, he says. While the extract is extremely effective against bacteriophage, inactivating nearly 100% of viral particles based on plaque assays, it shows no antibacterial effects, he adds. “Based on electron microscopy images, we posit that the in-

Ginger is among the natural products found to have antimicrobial activity. It contains a sugar that inhibits growth of *P. aeruginosa* biofilms. (Image © egal/iStockphoto.)
activation of the virus is due to degradation of the viral capsid.”

Shannon Weiman is a freelance writer in San Francisco, Calif.

ASM MEETING

**Persistor Bacteria: Part of a Peculiar Four-Season Cycle or Mere Zombies?**

Jeffrey L. Fox

Tempting as it is to endow living bacteria with human traits, it may be even more tempting to call them subhuman “zombies” when they cease growing, stubbornly persisting in a dormant state, and then either cease to do anything interesting or reactivate to cause greater havoc than before. Parts of this puzzling microbial behavior might be part of a more stately “four seasons” pattern of microbial life, according to Slava Epstein of Northeastern University in Boston, Mass., who spoke during the plenary session, “Zombie Microbes: Dormancy, Latency, and Persistence,” at the 2015 ASM General Meeting last May.

The dormancy of microbes fascinates Epstein. “The phenomenon was discovered 100 years ago, and maybe it’s the oldest unsolved problem” in microbiology, he says. “I became obsessed with it. I have had lots of ideas about it, but many of them don’t work. Then I had some new thoughts a few months ago.” Those comments summarize the genesis of his hypothesis describing the four seasons of microbial life, which he does not tie explicitly to summer, fall, winter, and spring, but instead likens to those surrounding it. That scout condition for “okay” could well be highly variable and very much dependent on the particular microbial species and the conditions surrounding it. That scout will grow to form a colony whose members then can somehow wake up the rest of the dormant population.

Epstein says this microbial cycle could be much like differentiation in multicellular organisms. “When a scout forms, it’s like specialization, and [a cell] going into dormancy is like de-differentiation—becoming again like a stem cell to survive and then reprogram itself,” he says. “I’m proposing a certain degree of differentiation in the microbial world. Is there any supporting evidence? Does de-differentiation occur during dormancy? I don’t know, and I have no data to support it.”

Notwithstanding the difficulties of proving the seasonal hypothesis, it may furnish useful insights into growing reluctant-to-cultivate microbial species, Epstein suggests. “The rule is, inocula need to be fresh, but our idea is the opposite.” Put another way, shock and adversity might provide valuable means for awakening dormant microbial newcomers. “What if we hit them hard, shock them, or starve them for a few weeks, then try to grow them on Petri plates?” he wonders. Now that it is summer, one can bet the answers to these questions will not become evident before or until the seasons change.

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

**MINITOPIC**

**Prions Help To Maintain Memories in Mice; Synthetic Prions Are Infectious**

Prion-like proteins are critical for maintaining long-term memories in the sea slug *Aplysia*, mice, and perhaps in other mammals, according to Luana Fioriti, Joseph Stephan, Luca Colnaghi, Bettina Drisaldi, and their collaborators, all working with Eric Kandel at Columbia University Medical Center in New York, N.Y. “When we learn something and form long-term memories, new synaptic connections are made, the soluble prions in those synapses are converted into aggregated prions,” Kandel says. “The aggregated prions turn on protein synthesis necessary to maintain the memory. This ongoing maintenance is crucial.” In this capacity, these functional prion proteins do not contribute to disease, according to Kandel and his collaborators. “There are probably other regulatory components involved,” he adds. “Long-term memory is a complicated process, so I doubt this is the only important factor.” Details appeared 17 June 2015 in *Neuron* (doi.org/10.1016/j.neuron.2015.05.021) and 23 June 2015 in *Cell Reports* (doi.org/10.1016/j.celrep.2015.04.061, doi.org/10.1016/j.celrep.2015.04.060, and doi.org/10.1016/j.celrep.2015.05.034). In a separate development, synthetic prions made in bacteria can cause disease that is “is pathogenically and pathologically identical to naturally occurring contagious transmissible spongiform encephalopathies,” according to Jiyan Ma, from the Van Andel Research Institute in Grand Rapids, Mich., and collaborators. Details appeared 2 July 2015 in *PLOS Pathogens* (doi:10.1371/journal.ppat.1004958). Nonetheless, the source of prions matters, and accurate modeling of inherited prion diseases “requires the expression of authentic mutant human PrP in transgenic models, as other approaches may generate results that do not mirror the human disease,” note John Collinge of University College London in London, United Kingdom, and his collaborators. Details appeared in that same issue of *PLOS Pathogens* (doi:10.1371/journal.ppat.1004953).
**MINITOPIC**

**Progress Notes for Novel and Nifty Methods and Diagnostics**

Examples of recent progress toward developing useful methods for genomic sequencing and for diagnosing diseases include:

- The Oxford Nanopore MinIONTM device, about the size of a cell phone, was used to determine the genomic sequence of _Escherichia coli_, with appropriate gene order (compared to previous analyses) and 99.5% nucleotide identity, according to Nicholas Loman from the Institute of Microbiology and Infection at University of Birmingham in Birmingham, United Kingdom, Jared Simpson of the Ontario Institute for Cancer Research in Toronto, Ontario, Canada, and their collaborators. Details appeared 15 June 2015 in _Nature Methods_ (doi:10.1038/nmeth.3444).

- A new software tool called ProDeGe (Protocol for Decontamination of Genomes) automates the removal of contaminating DNA sequence data from draft genomes, according to Kristin Tennesen, Nikos Kyrpides, and their collaborators from the Prokaryotic Super Program at the U.S. Department of Energy Joint Genome Institute in Walnut Creek, Calif. Details appeared 9 June 2015 in the _ISME Journal_ (doi:10.1038/ismej.2015.100).

- An inkjet-printable form of purified silk protein can be doped with antibiotics, gold nanoparticles, and bacteria-sensing polydiacetylene compounds, according to Fiorenzo Omenetto of Tufts University in Medford, Mass., and his collaborators there and at the University of Illinois at Urbana-Champaign. Details appeared 16 June 2015 in _Advanced Materials_ (doi:10.1002/adma.201501425).

- _Cryptosporidium_, a protozoan parasite that can cause severe diarrhea, was genetically engineered with a version of CRISPR/Cas9 to carry a reporter gene—that providing a means to screen candidate drugs when this strain is used to infect mice, according to Boris Striepen of the University of Georgia, Athens, and his collaborators. Details appeared 15 July 2015 in _Nature_ (doi:10.1038/nature14651).

**ASM MEETING**

**Through Peptidoglycan Complexes, Scaffold Proteins Set Cell Morphologies**

Shannon Weiman

Bacteria come in many different shapes, relying on peptidoglycan (PG)-based cell walls to provide structural integrity and apparently depending on scaffolding proteins to confer morphologic variety, according to several researchers who spoke during the plenary session, “The Envelope Please,” at the 2015 ASM General Meeting, held in New Orleans last May. These scaffold proteins are critical players, localizing PG synthesis complexes and directing them to generate specific cellular geometries.

One of these scaffolding proteins is MreB, an actin-like, cytoskeletal protein, without which bacteria develop irregular shapes, according to Rut Carballido-Lopez of the INRA in Jouy-en-Josas, France. Static images misleadingly suggest that MreB forms helical filaments to guide PG synthesis, she says. However, by viewing _Bacillus subtilis_ via specialized microscopy, she sees that MreB forms motile patches, assembling PG synthesis complexes and then orienting their movement circumferentially, perpendicular to the cell axis. PG synthesis powers the movement of these complexes, not polymerization of MreB as previously thought, she says. “These findings challenge the perceived functional similarity between MreB proteins and eukaryotic actins, raising again the question of mechanisms underlying MreB morphogenetic function.”

In addition to assembling the PG complexes, MreB also helps to organize intracellular complexes involved in precursor synthesis, according to Carballido-Lopez. “We propose a model in which MreB organizes intracellular steps of PG synthesis in the cytoplasm to feed the membrane-associated cell wall synthesizing machinery...coordinating (these processes),” she says.

Although these mechanisms are widely conserved among gram-positive and gram-negative bacteria, the two classes of bacteria regulate the processes differently, Carballido-Lopez finds. During exponential growth, which demands increased cell-wall synthesis, gram-negative _Escherichia coli_ cells upregulate MreB, increasing the numbers of assembly complexes. In contrast, gram-positive _B. subtilis_ cells retain the same number of such complexes, while increasing the speed at which they act in a way that is proportional to growth rate, she says. “These distinct mechanisms reflect different cell-wall integrity constraints in gram-positive versus gram-negative bacteria.”

Another scaffolding protein, SpmX, controls a particular morphological feature in the Caulobacteraceae family, according to Yves Brun of Indiana University in Bloomington. “Although bacteria exhibit a myriad of morphologies, the mechanisms responsible for the evolution of bacterial cell shape are not understood,” he says. “We investigated morphological diversity in a group of bacteria that synthesize stalks, tubular extensions of the cell envelope, including the peptidogly-
can. The location and number of stalks varies according to species—polar in the genus Caulobacter and subpolar or bilateral in the genus Asticcacaulis.”

In each of these species, the SpmX protein localizes to different subcellular positions before it recruits the PG synthesis machinery and directs it to form stalks. A variable domain of this scaffold protein specifically controls cell morphology, having diverged between species to find different targets. Meanwhile its C-terminus, which may recruit and activate PG synthesis machinery, is conserved among these several species.

Swapping this domain between species confers the morphology of the SpmX donor, according to Brun. “Stepwise evolution of a specific region of SpmX led to gain of a new function and localization, which drove the sequential transition in stalk positioning,” he says. “Our study has begun to unravel the elusive mechanisms of morphological transition in bacteria by showing that evolution of the SpmX morphogen underlies the evolutionary trajectory of stalk positioning.”

**NEW IN ASM JOURNALS**

*Wolbachia*-Infected Male Fruit Flies Are Less Feisty than Uninfected Peers

David C. Holzman

Male fruit flies infected with the bacterium *Wolbachia* are less aggressive than are uninfected hosts, according to Jeremy Brownlie of Griffith University in Brisbane, Australia, and his collaborators. He says that this is the first time bacteria were observed influencing aggressive behavior in an animal. Details appeared in the July 2015 *Applied and Environmental Microbiology* (doi:10.1128/AEM.00573).

Elizabeth Bondy, an undergraduate student from the University of Arizona who was being trained to handle fruit flies in Brownlie’s lab, noticed that those infected with the wMelPop strain of *Wolbachia* were less aggressive than their uninfected peers. For instance, infected flies took three times longer than others to start a fight. Even so, their bouts lasted as long as fights among uninfected peers.

Researchers find that infection with *Wolbachia* bacteria affect production of the neurotransmitter octopamine in fruit flies, resulting in lowered aggression. (Image © janeff/iStockphoto.)

**MINITOPIc**

Microbiology Policy Bulletin Board

Recent national and international developments involving microbiology and related science policy matters include:

- California legislators passed and governor Jerry Brown signed legislation eliminating exceptions and thus mandating children to be vaccinated against 10 specific infectious diseases and “any other disease deemed appropriate.” Although the new law eliminates earlier exemptions that were based on parental objections to vaccine use, it explicitly provides for physicians to grant exceptions when warranted.

- The U.S. House of Representatives in July approved the 21st-Century Cures Act, which seeks higher funding for the National Institutes of Health and the Food and Drug Administration, and also would encourage patient-focused drug development, the development of precision medicine, greater FDA flexibility, extra support for young scientists, and special provisions regarding antimicrobial products and also medical devices. A version of this bill is under development in the Senate.

- In June, several U.S. Senators introduced the “Lyme and Tick-Borne Disease Prevention, Education, and Research Act of 2015,” which would educate the community about such diseases, encourage development of better diagnostics, and take other steps to organize and strengthen research on these diseases.
Diets Deduced from Dental Plaque from Paleolithic Hominins

The dietary habits of ancestral humans—hominins—from the middle Pleistocene can be deduced, at least in part, by analyzing plaque scraped from their teeth, according to Karen Hardy at the Universitat Autònoma de Barcelona in Spain and her collaborators at the University of York in the United Kingdom and Tel Aviv University in Israel. Based on chemical and optical analyses, plaque samples from the remains of three individuals found in Qesem Cave, Israel, contained starch granules and chemical compounds that are consistent with a diet of plants, probably nuts and seeds, rather than meat, they report. The plaque analysis also provides evidence of respiratory irritants and allergens, including fungal spores and pollen, while plant fibers and wear patterns on the teeth point to chewing of raw materials—and, possibly, hygiene activities such as tooth picking (but not flossing).

“Dental calculus from human teeth of this age has never been studied before, so we had very low expectations because of the age of the plaque,” says Hardy’s collaborator Ran Barkai, of Tel Aviv University. “However, because the cave was sealed for 200,000 years, the teeth we analyzed were exceedingly well preserved.” Details appeared 18 June 2015 in Quaternary International (doi:10.1016/j.quaint.2015.04.033).

their uninfected counterparts, meaning this gentler behavior was not due merely to Wolbachia-induced sickness, Brownlie says.

Because the neurotransmitter octopamine regulates fruit fly aggression, Brownlie and his collaborators anticipated that the infected flies produce less of the compound than their uninfected peers. Octopamine measurements support that view, as does the fact that expression of two genes that encode enzymes responsible for producing octopamine are present at lower levels in infected flies. “That suggested that Wolbachia directly affects fruit fly gene function,” he says.

Wolbachia bacteria infect 40% of insect species as well as other invertebrates, but not vertebrates. These bacteria affect host reproduction, alter sex selection among host offspring, and can be transmitted directly from parents to host offspring. They also influence host metabolic pathways, protect hosts from pathogens, influence lifespan, and may play a role in speciation, according to Brownlie.

“Reports of Wolbachia’s ability to manipulate host behavior are rare,” despite clear evidence of its ability to infect nervous tissue, says Beth McGraw of Monash University in Clayton, Victoria, Australia. Moreover, the only type of Wolbachia that reduces aggression among fruit flies is a laboratory strain, according to Wolfgang J. Miller of the Medical University of Vienna in Austria. “There is even a fitness cost for males carrying this infection type, and hence it is quite likely that the wMelPop [strain] will never be found in nature,” he says. Nonetheless, Brownlie’s research is important “since it beautifully shows no adaptive behavioral effects that would increase the fitness of infected males for natural infections in [fruit flies].” This finding “is good news for fruit fly neurobiologists, who can stop worrying that some Wolbachia might affect their behavioral assays.”

The wMelPop strain of Wolbachia that Brownlie and his collaborators are studying can be stably transferred into mosquitoes, a capability that is part of a larger program to use these insects as an agent for controlling the spread of the dengue virus, McGraw points out. However, she says, if this strain leads to a similar reduction in aggression among male mosquitoes that Brownlie sees in fruit flies, that lowered aggressiveness could hinder the spread of the dengue control agent among mosquitoes in the wild.

David C. Holzman is the Microbe Journal Highlights Editor.

NEW IN ASM JOURNALS

Key Methanococcus Electron Transfer Enzymes Can Work Outside Cells

Barry E. DiGregorio

Enzymes from microorganisms such as Methanococcus maripaludis and Sporomusa sphaeroides can interact directly with nearby solid surfaces, taking up electrons and forming intermediates that the cells quickly consume, according to Jörg Deutzmann, Merve Sahin, and Alfred Spormann from Stanford University in Stanford, Calif. This process could be “an ecologically important but so far overlooked mechanism in biological electron transfer,” they say—one with an important impact on electrosynthesis but also on microbially induced corrosion, which leads to losses of more than $1 billion per year. Details appeared 21 April 2015 in mBio (doi:10.1128/mBio.00496–15).

Determining this mechanism was no easy task, Deutzmann says. Finding that “regular enzymes” can bind a cathodic surface and catalyze a reaction outside the cell is a “major discovery,” he says. “Knowing the mechanism allows for targeted improvement of this mechanism, which, in turn, might lead to more efficient microbial electrosynthesis systems. From an engineering perspective, it makes a difference if you have to design an electrode to accommodate large microbial cells versus enzymes. You can attach a lot more enzymes to the electrode, because enzymes are significantly smaller.
“At first, we were searching for a direct electron uptake mechanism that is similar to what has been proposed for other organisms like *Geobacter* and *Shewanella,*” Deutzmann continues. “This was the easiest explanation, but we never found clear evidence.” Instead, their experiments indicate that cells first release enzymes, which bind to cathode surfaces, where they take up electrons and use them to form small, readily diffusible compounds, including hydrogen and formate, that the cells very quickly consume and metabolize further. Hydrogenase and other enzymes take up electrons directly from the electrode surface, but the microbial cell itself is not involved in the transfer, in contrast to what was widely assumed.

Extracellular redox-active enzymes also play a role in causing iron to corrode. When the enzymes contact iron, it can transfer electrons directly to hydrogenase, according to the Stanford scientists. The enzyme uses these electrons to make hydrogen molecules, which, in turn, are consumed by methanogens.

One long-term goal is to “create large bioreactors where microbes convert atmospheric carbon dioxide and clean electricity from solar, wind, or nuclear power into renewable fuels and other valuable chemicals,” Spormann says. One major challenge, however, is to rid oxygen from that carbon dioxide before converting it into methane, Deutzmann adds.

“Microbes have evolved many different ways to interact with metals and minerals,” says Tom Clarke at the University of East Anglia in the United Kingdom. “While . . . *Geobacter* and *Shewanella* are renowned for their ability to directly reduce their mineral substrates, [the Stanford group] convincingly showed that methanogenic, metal-eating bacteria actively secrete enzymes that oxidize the iron, generating hydrogen that the microbe can then get energy from, drawing analogies to a farmer sowing seeds that will later produce fruit.”

Barry E. DiGregorio is a freelance writer in Middleport, N.Y.

**NEW IN ASM JOURNALS**

**Messenger Molecule Boosts Biofilm Formation in Bladder, Kidneys**

*Pseudomonas aeruginosa* produces a messenger molecule that encourages the bacteria to colonize catheters in the bladders of laboratory mice, where they form biofilms, according to Stephanie Cole and Vincent T. Lee of the University of Maryland, College Park. Normally, absent surfaces that encourage biofilm formation, few bacteria inhabit the bladder or kidneys. In earlier work, these and other investigators showed that the messenger molecule, cyclic-di-GMP, promotes biofilm formation when such surfaces are present. In the current study, infecting catheterized mice with *P. aeruginosa* producing high c-di-GMP moderately boosted the number of bacteria in the bladders and kidneys. Conversely, infecting the mice with *P. aeruginosa* producing low c-di-GMP substantially reduced those numbers. (It’s safe to assume that bacteria being detected were largely in biofilms, says Lee.) One mystery: c-di-GMP influences biofilm formation by acting on pili, flagella, and extracellular polysaccharide. But Lee found that mutant bacteria unable to make pili and flagella could still infect the mice. Thus, he says, c-di-GMP must be acting on an unknown target to influence biofilm formation. Discovering that target could aid the development of more effective therapies, he says.


**NEW IN ASM JOURNALS**

**Towards a Universal Flu Vaccine**

Jeffery Taubenberger et al. of the National Institute of Allergy and Infectious Diseases, National Institutes of Health show that a universal influenza vaccine might provide broad protection against numerous influenza strains, in lieu of annual development of new vaccines targeted at specific strains predicted to be the most common in a given year. The investigators used a virus-like particle vaccine cocktail that expressed hemagglutinin H1, H3, H5, and H7. Sixteen hemagglutinin subtypes that circulate in birds are thought to be the basis for current and future influenza pandemics, says Taubenberger. “The hypothesis was that the presentation of these different viral proteins would stimulate development of cross-protective immunity that would provide broader protection against multiple subtypes.” In the study, 95% of mice vaccinated with the investigational cocktail were protected from lethal challenge with eight different influenza strains expressing seven different influenza A subtypes, while only 5% of controls survived.


**NEW IN ASM JOURNALS**

**Cystic Fibrosis Microorganisms Survive on Little to No Oxygen**

Cystic fibrosis causes thickened mucus in the airways, leaving sufferers susceptible to chronic lung infection. Now Wiebke Ziebis of the University of Southern California and Dianne K.
Newman of the California Institute of Technology, Pasadena, et al. show that microbes contributing to cystic fibrosis can survive in saliva and mucus that is chemically heterogeneous, including in portions largely devoid of oxygen. The microbiologic environment can differ between patients, and even within a patient at different points in time, these investigators report. “The diversity and adaptation of disease-causing microorganisms within the CF lung environment is what renders CF infections so difficult to eradicate,” says Newman. Few studies have characterized the chemistry of mucus within CF airways, but such measurements are critical to understanding the survival of microbes and their impact on this microenvironment, she added. Further study is needed to determine whether particular metabolic fingerprints correlate with disease progression and, if so, which treatments would be most effective under various conditions.


NEW IN ASM JOURNALS

Investigators Warn against Tetracycline in Bee Hives

In contrast to the low diversity of the honeybee gut microbiome, the hive is home to diverse species, including many lactic acid bacteria. Irene L. G. Newton and colleagues of Indiana University, Bloomington, sampled lactic acid bacteria communities found across hive environments, and identified interactions between non-core bacterial members, notably Fructobacillus and Lactobacillus, and honeybee specific core members. “Co-culture assays showed that these non-core bacterial members promote the growth of honey bee specific bacterial species,” Newton et al. write, alluding to the promotion of honeybee gut community members in vitro by Fructobacillus and its byproducts. Of particular note, the investigators found that Fructobacillus, which they think may be important for establishment of the microbiome, is sensitive to the commonly used antibiotic tetracycline, and recommend that use of the drug should be limited.


NEW IN ASM JOURNALS

New Bioreactor Enables Study of Bacterial Growth Under Extremes of Pressure and Temperature

Continuous culture under elevated pressures is an important technique for exploring microbial growth and survival in extreme environments associated with the deep biosphere. Now, in a pilot experiment, Dionysis I. Foustoukos and Ileana Pérez-Rodríguez of the Carnegie Institution of Washington, D.C., have fermentatively grown the thermo-piezophilic bacterium, Marinitoga piezophila for 382 hours at 65°C, and at pressures ranging from 0.1 to 40 MPa, while varying medium flow rate from 2 to 0.025 ml/min. The bioreactor can withstand temperatures from 25 to 120°C and pressures of 69 MPa, and enables use of medium enriched in dissolved gases, under aerobic or anaerobic conditions, while allowing sampling of incubated organisms with minimal physical/chemical disturbance within the reactor. “We anticipate that this technology will accelerate our understanding of the physiological and metabolic status of microorganisms under temperature, pressure, and energy regimes resembling those of Earth’s piezosphere,” the investigators write.


NEW IN ASM JOURNALS

Host Factors Can Alter Prion Phenotypes

Prions are misfolded pathogenic proteins that cause neurodegeneration in humans and animals. Transmissible prion diseases exhibit a spectrum of disease phenotypes. The basis of this diversity is encoded in the structure of the pathogenic prion protein and propagated by an epigenetic mechanism. Richard A. Bessen of Colorado State University, Fort Collins, et al. investigated prion diversity in two host species that express the same prion protein gene. “While prior reports have demonstrated that prion strain properties are stable upon infection of the same host species and prion protein genotype, our findings indicate that certain prion strains can undergo dramatic changes in biological properties that are not dependent on the prion protein,” but rather on host-dependent factors, writes Bessen. Knowledge of how host pathways can modify prion disease phenotypes, he adds, could provide clues on how to alter prion formation that could lead to treatments for prion diseases and other neurodegenerative diseases caused by protein misfolding.

Challenges of Antibiotic Discovery

Antibiotic resistance and tolerance plus troubles with discovery platforms complicate efforts to identify useful antibacterial drug candidates

Kim Lewis

It is hard to discover new antibiotics. The field of antiinfectives has a unique history which does not follow the expected path of knowledge leading to cures. We now know incomparably more than we did during the golden era of antibiotic discovery from the 1940s to 1960s, but seem no longer capable of developing novel therapeutics for infectious diseases. Why this anomaly? What approaches can revive antibiotic discovery?

Alexander Fleming discovered penicillin, the first truly successful antibiotic, when he noticed that a contaminating Penicillium fungus was killing staphylococci on a Petri dish. Finding this antibiotic was a rare event, a lucky strike, but that changed when Selman Waxman pioneered systematic screening, revolutionizing the field, and with it, the entire pharmaceutical industry.

Streptomyces are the most prolific antibiotic producers, and Waxman recognized their potential. He introduced a simple screen which essentially replicates the accidental observation of Fleming—a Streptomyces is spot-inoculated on a plate with a lawn of a test pathogen, and a zone of growth inhibition indicates presence of an antibiotic. This method soon resulted in the discovery of streptomycin from Streptomyces griseus. Streptomycin became the first antibiotic capable of treating infections by gram-negative bacteria and the first effective treatment for tuberculosis. The subsequent discovery of tetracycline, erythromycin, and vancomycin which followed transformed the pharmaceutical industry (Fig. 1). Resistance to most antibiotics appeared soon after their discovery, but this was a relatively minor issue at the time given the constant flow of new compounds.

What happened next, however, was completely unexpected. No new class of broad-spectrum antibiotics was discovered in the next 50 years, and pathogens continue acquiring resistance. We now face strains of pathogens, such as Mycobacterium tuberculosis and Acinetobacter baumanii, resistant to all known antibiotics.

A New Threat—Drug Tolerance

Advances in medicine can provide favorable environments for pathogens. Biofilms grow on indwelling devices such as catheters, orthopedic prostheses, and heart valves and are hard to kill, which is puzzling, since most chronic infections are caused by drug-susceptible pathogens.

Time-dependent killing of biofilms explains this paradox—most of the population dies, but a small number of persister cells survive.Persisters are dormant variants of regular cells that biofilms protect from the immune system. When antibiotic concentration drops, persisters revive, causing a relapsing infection.

Tuberculosis (TB) is an analogous case of a difficult-to-treat infection, requiring months of therapy. M. tuberculosis hides within macrophages, shielded from the immune system, and dormant cells play an important role in the recalcitrance of the infection. Bactericidal antibiotics kill by corrupting their targets—for example,
fluoroquinolones convert DNA gyrase into an endonuclease, and aminoglycosides interrupt translation, which results in misfolded toxic peptides. In a dormant persister, targets are largely inactive, leading to antibiotic tolerance.

Isolated persisters overexpress toxin/antitoxin (TA) modules, pointing to a possible mechanism. Toxins inhibit important functions, such as protein synthesis, sending cells into dormancy. There are over 20 TA modules in *Escherichia coli*, and over 80 in *M. tuberculosis*. The reason for this high level of functional redundancy is unclear. We found that a particular toxin, TisB, is expressed by the SOS response during DNA damage which can be caused by fluoroquinolone antibiotics. TisB forms an ion channel in the membrane, leading to a dissipation of the pmf and ATP, producing a dormant state. Overexpression of several TA modules leads to an increase in persisters when *Salmonella typhimurium* enters human cells, according to Sophie Heaine and coworkers at the Imperial College London, though the nature of the trigger is unknown. This analysis shows that in persisters, we are facing an ultimate adversary—cells that evolved specifically to survive exposure to antimicrobials. They employ multiple redundant pathways, so that there is no realistic antipersister target; being in a low-energy, dormant state confers tolerance to all currently available antibiotics.

**Unique Challenges in Discovering and Developing Antibiotics**

Antibiotics are both uniquely effective and uniquely difficult to develop. The relative ease with which the main classes of antibiotics were discovered during the golden era is not surprising, these compounds evolved to effectively kill bacteria. Interestingly, during that same period, a number of synthetic compounds were also introduced. These still make up the main anti-TB armamentarium—isoniazid, pyrazinamide, ethambutol, and ethionamide. Metronidazole, a broad-spectrum compound effective against pathogens living under anaerobic and microaerophilic conditions, was discovered as well. Nalidixic acid, a rather weak agent, was developed into a remarkably successful class of broad-spectrum fluoroquinolones. So when the natural product pipeline dried up, many expected discovery to simply shift to synthetic compounds; however, this did not happen. Before we consider how to revive discovery, let us consider some
obstacles on the way to developing new antibiotics.

- **Penetration.** Bacterial cells are exposed, and evolved a penetration barrier which is particularly effective in gram-negative species, in which the outer membrane is covered with negatively charged lipopolysaccharide, restricting access to hydrophobic compounds. The inner membrane blocks hydrophilic compounds, while multidrug pumps (MDRs) expel compounds that penetrate both the inner and outer membranes. The envelope is an almost impenetrable barrier for drugs.

- **Toxicity.** Largely due to difficulty of penetration, effective concentrations of antibiotics are in the micromolar range, as compared to nanomolar range for therapeutics acting against targets in mammalian cells. The need for high doses leads to off-target action and toxicity. For example, aminoglycosides inhibit protein synthesis, but like other polycations, they accumulate in the lysosomes of kidney cells and cause nephrotoxicity at clinically effective doses.

- **Multiple pathogens.** Most antibiotics need to act against more than one pathogen, meaning that a single compound needs to effectively hit multiple members of an orthologous group. This single compound is also supposed to penetrate into cells with different sets of MDRs.

- **Resistance development.** Resistance by target modification occurs with a probability of about $10^{-9}$ to $10^{-8}$. If a patient has an infection involving around $10^9$ cells, resistance will cause therapy failure, making development of such an agent with a single target impractical. Compounds belonging to the main classes of currently used antibiotics—β-lactams, aminoglycosides, macrolides, tetracyclines, and fluoroquinolones—effectively hit multiple targets, retarding development of resistance.

- There are also additional barriers unrelated to science that are hard to overcome:

- **Profit.** Antibiotics are victims of their own success because they produce effective cures; this, paradoxically, makes them less attractive than compounds that do not cure at all. A single dose of oritavancin is sufficient to cure acute bacterial skin and skin structure infection caused by *S. aureus*; a single dose of ceftriaxone cures gonorrhea (of course, if the pathogens are susceptible). But cholesterol-lowering statins, for example, do not cure the underlying cause of disease and have to be taken for a lifetime. According to IMS Health, the best-selling antibiotic is the narrow-spectrum daptomycin (Cubist/Merck); at number 94 among all drugs, it grosses $670 million per year and sales are projected to reach $1 billion. At number 1 is Abilify, an antidepressant, making $7.7 billion per year.

- **Public interest.** Chronic diseases cause prolonged suffering for patients and their families. This suffering results in high public awareness; there are many foundations dedicated to combating cancer, and there are well-organized and well-funded organizations dedicated to heart disease, Crohn’s and colitis, Huntington’s disease, and other conditions. Though a considerably larger number of people die from infectious diseases than from Huntington’s, there is no grant-giving foundation to support work on antibiotics in general, or rallies to combat drug-resistant pathogens. As with other diseases, there are foundations focused on specific chronic infections, such as the Gates Foundation and the Global TB Alliance support work on tuberculosis, the Cystic Fibrosis Foundation funds work on pathogens associated with this disease, and the Global Lyme Alliance supports work on Lyme disease. It should therefore be possible to communicate the significance of the larger issue of the importance of antibiotic discovery to the public. This is starting to happen in Great Britain, where the public has named antibiotic resistance among the five major public health priorities. The European Union established a large public-private partnership program to combat antibiotic resistance. In the United States, the President has recently issued an Executive Order for establishing a strategic program to combat antibiotic resistance (see *Microbe*, August 2015, p. 313).

### Discovery Platforms

Since the Waxman platform for drug discovery collapsed, we have been struggling to replace it. As a result of the absence of a platform capable of reliably supplying leads, virtually all novel classes of antibiotics introduced in the last decades, including synercid, daptomycin, linezolid, and fidaxomycin, came from resuscitating old failed leads. There is consensus that the lack of good starting compounds is the bottleneck that limits the rate of developing novel antibiotics.

Before we consider platforms that can be developed, we should determine the knowledge gaps preventing their development. There are two general categories of molecules from which
antibiotics can be discovered: natural compounds and synthetics. For natural compounds, uncultured bacteria and silent operons are two untapped sources of secondary metabolites, and it would be useful to know how to access these. For synthetics, we need to know what determines the ability of a compound to penetrate into bacterial cells.

**Rules of penetration.** We know from long experience that screening of compound libraries does not produce good antimicrobial agents with a reasonable spectrum. The penetration problem makes rational design of inhibitors against particular targets very difficult. Substantial progress has been made in studying the structure of the MDR pumps of bacteria, but what we learned is not useful for designing penetrating compounds—the large, poorly structured binding sites of the model AcrAB-TolC pump of *E. coli* can accommodate a vast variety of chemically unrelated compounds.

Determining the rules of penetration, similar to the Lipinski rules that have been highly valuable in selecting orally bioavailable compounds that hit mammalian targets, is important. The Lipinski rules were formulated by culling useful properties from a large set of known drugs. We could similarly establish rules of penetration for antibiotics, based on a large number of compounds that penetrate into cells of gram-negative bacteria. Penetration of compounds from a random library can be measured using mass spectroscopy. Some insights into penetration rules can be gleaned even from the small set of good permeators we currently have. Highly hydrophobic compounds are well recognized by MDRs, while relatively hydrophilic compounds that are less than 450 Da are favored for penetration; zwitterions penetrate well; and it seems that inclusion of atoms that do not occur frequently in natural compounds (F, B) is good for penetration.

Once the rules are established, libraries specifically compiled for antimicrobial discovery can be synthesized. The rules would also be helpful in rational design based on the crystal structure of targets. The ligand could not only be optimized for good binding, but for penetration as well.

**Reviving the Waxman platform.** Uncultured bacteria, organisms that previous generations of prospectors would not have seen on their Petri dishes, are perhaps the most promising source of secondary metabolites. Based on metagenomic analysis, 99% of all microbial species on the planet are “uncultured” and do not grow under laboratory conditions, and this is a potential source of hidden antimicrobials. For example, a recently described *Entotheonella* sp. is responsible for making a dozen different antimicrobials present in a marine sponge. The diversity and number of compounds isolated from this single bacterium suggests that *Entotheonella* may represent a genus comparable to Streptomycetes in its ability to produce antimicrobials.

While *Entotheonella* has not yet been cultured, a general method for growing uncultured bacteria has been developed. The gist of the approach is to grow bacteria in their natural environment by introducing a marine sediment or soil sample diluted with agar between two semipermeable membranes, and placing this “diffusion chamber” back into the natural environment. Compounds diffuse freely through the chamber, and bacteria are tricked into perceiving it as their natural environment. This approach dramatically improves recovery; up to 40% of cells seeded into the chamber produce colonies.

A common cause of “uncultivability” is a need for growth factors produced by neighboring bacteria. Iron-chelating siderophores are one important group of such factors in the marine sediment environment. Repeated reinoculation from chamber to chamber results in “domestication” of a considerable proportion of uncultured microorganisms, an ability to grow on a Petri dish or in a fermenter. Interesting compounds are starting to emerge from this approach (described below), showing the promise of the platform.

**Silent operons.** Another untapped source of antimicrobials may be in the silent operons of producing microorganisms. The genomes of Actinomycetes show that their potential for producing secondary metabolites far surpasses their known ability. Enzymes producing antimicrobials—the polyketide synthases and nonribosomal peptide synthases—are encoded by large operons with homologies to known genes. Sequencing of the model Actinomycete *Streptomyces coelicolor* showed that it codes for 20 secondary metabolites, while it is known to produce only 3 antimicrobials. *S. avermitilis*, the industrial producer of the antihelminthic avermectin, does not make antimicrobials at all (at least not in the lab), but according to its genome sequence, harbors 30 operons for secondary metabolites. This general theme of numerous silent operons holds for the many additional actinomycete genomes that
have since been sequenced. This is a platform waiting to be developed, though we do not yet have good approaches to efficiently turn on production of silent operons.

Interesting Compounds in Discovery and Development

There are several novel compounds at different stages of development which act against new targets. The oxaborole AN3365 (Anacor/GSK) (Fig. 2A), an effective inhibitor of the leu-tRNA synthase, is small and fairly polar, and penetrates well into gram-negative bacteria. Though it failed in Phase II clinical trials due to resistance readily developed by mutations in the target, AN3365 is an excellent example of how to make a well-penetrating molecule and is a promising compound for combination therapy.

POL7080 (University of Zurich/Polyphor/Roche) was discovered by a lucky accident in a program aimed at producing mimetics of the membrane-acting antimicrobial peptide (AMP) protegrin. The target is not the cytoplasmic membrane but LptD, a β-barrel protein of the outer membrane of P. aeruginosa (Fig. 2B) that participates in inserting lipopolysaccharide into the outer membrane. Since the target is on the surface of the cell, there are no permeability issues. Even though it is a single target, the frequency of mutations in LptD is very low, probably because POL7080 is a large compound with multiple binding interactions. POL7080 is specific against P. aeruginosa, but other antimicrobials targeting the conserved LptD protein are likely to follow. Species selectivity has its advantages; for one, the compound will not harm our microbiome. POL7080 is being developed as an anti-pseudomonas drug and is in Phase II clinical trials.

Lassomycin (Northeastern/NovoBiotic) was identified in a specific screen of a collection of uncultured bacteria against M. tuberculosis and is produced by Lentsea, an actinomycete. Extracts were countergenerated against S. aureus, and only specific hits against M. tuberculosis were followed. Since virtually no natural products are specific against mycobacteria, this simple screen allows one to determine extracts containing novel compounds before doing any chemistry, avoiding the bottleneck of sorting known and toxic compounds that slows down natural product discovery. Lassomycin is a lasso-shaped peptide that inhibits the essential ClpP1P2C1 protease of M. tuberculosis while increasing its ATPase activity (Fig. 2C). This dual mode of action kills growing and dormant cells of the pathogen. The compound also serves as proof-of-concept for species-selective screening as a new antimicrobial discovery platform.

M64, benzamide-benzimidazole is an inhibitor of MvfR, the transcriptional activator of the P. aeruginosa quinolone quorum sensing (QS) regulon (MGH/Spero Therapeutics/Roche) (Fig. 2D). M64 is an optimized analog of a compound identified in a high-throughput screen of commercial libraries (the Harvard ICCB collection). QS controls virulence in this pathogen. M64 decreased persister formation in an exponentially growing culture of P. aeruginosa and improved survival of mice with a lung and wound infection. The in vivo efficacy of M64 was especially pronounced in combination with ciprofloxacin. Its discovery in a high-throughput screen suggests that commercial libraries that failed to produce compounds with a broad spectrum may harbor useful molecules acting against a single target. The promise of antivirulence factors lies in the expectation that they could have a low probability of resistance development. The discovery of M64 bodes well for two emerging platforms—species-specific compounds and antivirulence factors.

Acyldepsipeptide, developed by Bayer (ADEP4) but dropped due to high frequency of resistance, activates the ClpP protease (Fig. 2E). ClpP uses ATP-dependent chaperones to degrade misfolded proteins. Because ADEP keeps the entrance channel of ClpP open, no chaperones are needed. ADEP/ClpP is effective against energy-depleted persisters since it does not require energy to cleave proteins. We found that ADEP4 kills S. aureus persisters by forcing cells to self-digest. Since ClpP is nonessential, null mutants resistant to ADEP4 arise with high probability, but combining ADEP4 with another antibiotic solves this problem and leads to eradication of a biofilm population in vitro and in a mouse model of infection. Advanced analogs of ADEP4 are in development. ADEP is the first antibiotic that effectively kills persisters.

Teixobactin (NovoBiotic/Northeastern University) is a novel inhibitor of cell wall biosynthesis that was discovered in a screen of uncultured bacteria (Fig. 2F) (Microbe, April 2015, p. 138). It is produced by Eleftheria terrae, a β-proteobacterium belonging to a new genus. Teixobactin
Novel antibiotics in development. (A) The oxaborole (Anacor/GSK) inhibits the leu-tRNA synthase of gram-negative bacteria. Shown is the adduct that AN2679 (analog of the developmental lead AN3365) forms with tRNA in the LeuRS-tRNALeu cocrystal structure. (B) A peptidomimetic L27-11 (close analog of the lead POL7080) inhibits LptD, a component of the lipopolysaccharide translocation machinery. (C) Lassomycin, a lasso-fold peptide produced by Lentsea, inhibits the ClpC subunit of the mycobacterial ClpP1P2C1 protease and activates its ATPase activity. (D) M64, benzamide-benzimidazole inhibits the quorum sensing regulator of MvfR which controls virulence of *P. aeruginosa*. (E) ADEP4 activates the ClpP protease, dissociating it from energy requirement. (F) Teixobactin, a depsipeptide produced by a β-proteobacterium *Eleftheria terrae*. Teixobactin binds lipid II, precursor of peptidoglycan, and lipid III, precursor of wall teichoic acid.
binds the lipid-pyrophosphate-sugar moiety of lipid II, precursor of peptidoglycan, and lipid III, precursor of wall teichoic acid in gram-positive bacteria. Since its targets do not mutate, there is no resistance development to teixobactin. Sophisticated resistance mechanisms such as destruction of the antimicrobial usually originate in the producing organisms, but E. terrae is a gram-negative bacterium that protects itself by exporting teixobactin across its outer membrane, and there is no such resistance mechanism for the targeted gram-positive organisms to borrow. It appears that teixobactin evolved to be essentially free of resistance. The discovery of teixobactin challenges the dogma of inevitable resistance.

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Suggested Reading


Allies and Adversaries: Roles of the Microbiome in Infectious Disease

Studying how nonnative pathogens and host-associated microbial communities interact help us better understand infectious diseases

Jessica Miles, Jonathan F. Holt, and Jo Handelsman

Recent studies of host-associated microbial communities highlight how little we know about the roles played by microbial residents during infections. Historically, research on pathogenesis neglected the roles of resident communities within which most pathogens function. Indeed, many researchers eliminate the native microbial communities of their model hosts to simplify analysis of pathogens that infect them. Because interest in the involvement of those communities in host health centers largely on how they modulate host defenses, more effort is needed to address the purely microbial interactions that influence how pathogens affect those microbial communities as they also colonize their hosts.

Differences among pathogens, commensals, and mutualists are blurred and context dependent. A bacterium that is beneficial in one tissue can prove pathogenic in another. Benign members of the resident microbial community can become aggressive pathogens when that community is disrupted. Therefore, forcing host-associated microorganisms into rigid functional groups is counterproductive. Rather, we prefer using the term, “microbiont,” which imputes neither beneficial nor harmful characteristics, capturing only a microorganism’s association with its host.

Here we explore two roles of resident microbes during pathogenesis. First, we survey evidence for host-associated microbial communities as barriers to infection and review current efforts to identify mediators of this protective function. Second, we examine how disrupting the microbiota can transform commensal residents into pathogens.

Microbial Communities Block Some Infections

More than a century ago, the Russian microbiologist and Nobel Laureate Ilya Metchnikoff uncovered evidence of colonization resistance, the ability of microbial communities to resist pathogens. When he consumed lactobacilli in sour milk, he learned that they did not survive for very long within his gut community and needed to be replenished frequently to exert salubrious effects on his health. American scientists Christian Herter (1865–1910) and Arthur Kendall (1877–1959) reinforced Metchnikoff’s work, reporting that lactobacilli do not survive after being introduced into the monkey gut.

Many subsequent studies of probiotics substantiate the challenge of establishing new strains of bacteria in the mammalian gut. In general, levels of newly introduced bacteria drop to undetectable levels within days. Thus, microbial communities apparently withstand challenges from nonnative microorganisms, suggesting that host tissues that harbor a resident microbiota resist further colonization.

SUMMARY

➤ Studies of bacterial pathogens should consider more fully how the host microbiome contributes to pathogenesis.

➤ Microbial residents of a host can act as a barrier to invasive pathogens.

➤ The idea that disrupting host-associated microbial communities spurs a commensal-to-pathogen switch needs further study.

➤ A comprehensive understanding of how resident communities promote or prevent commensal-to-pathogen switching could lead to new treatment strategies.
Handelsman: from a Focus on Microbial Communities to White House Science Policy

Jo Handelsman loves research so deeply that she nearly turned down an offer to work at the White House Office of Science and Technology Policy (OSTP), advising President Obama on scientific issues. "I couldn't imagine being away from bacteria, experiments, and students for two years," she says. Nonetheless, she accepted the offer to become associate director for science at OSTP in June 2014. "I absolutely love what I'm doing," she says. "People are inspiring and driven by the hope of making a difference in people's lives. I am thrilled to have the chance to contribute to that progress, particularly in the areas of microbiology, agriculture, public health, forensic science, and education."

Handelsman, 56, is on leave from Yale University, where she is the Howard Hughes Medical Institute Professor and Frederick Phineas Rose Professor in the department of molecular, cellular, and developmental biology. "Despite missing my lab and my students terribly, this is a chance of a lifetime to make a difference, and I intend to work as hard as I can to do just that, and then return to my research, no doubt with a new perspective," she continues. "My lab members have been absolutely wonderful about this period."

At Yale, Handelsman focuses her research on microbial communities, specifically how microorganisms interact with each other, and with hosts and inert surfaces. "We use both genetics and genomics, utilizing mutant analyses to identify genes that enhance or detract from success in a community," she says. "We also are interested in antibiotics, both in their native microbial community environment to understand their role in nature, as well as in antibiotic discovery and resistance for improving management of human infectious disease."

Handelsman, who "fell in love with microbiology in 7th grade looking at paramecia under a microscope," grew up in and around New York, N.Y. She received a B.S. from Cornell University in 1979 and a Ph.D. in molecular biology from the University of Wisconsin-Madison in 1984. Before joining Yale, she was professor of plant pathology at the University of Wisconsin-Madison from 1985 to 2009, and professor and chair of its department of bacteriology from 2007 to 2009. She served as president of ASM in 2013.

Handelsman, who has a keen interest in the status of women and minorities in science, rues "the talent we are missing due to explicit and implicit biases," she says. Several years ago, she and her colleagues sent a fictitious student resume to professors in biology, chemistry, and physics departments at six top universities, asking them to evaluate an imaginary candidate—randomly assigned the name John or Jennifer. "The results were stark and highly significant, both statistically and socially," she says. "The faculty would be more likely to hire John, pay him 15% more, believed he was more competent, and would be more likely to mentor him than Jennifer, although they liked Jennifer better."

Handelsman is married to Casey Nagy, a lawyer and anthropologist who is chief of staff for the president of the new Yale-National University of Singapore College. "He has been in Singapore full time since 2013, so . . . it will be nice to have him back in the States and even better when we are living in the same house again," she says. "I'm not sure I remember what a hobby is . . . But I used to garden, and still read and lift weights to maintain sanity."

Marlene Cimons

Marlene Cimons lives and writes in Bethesda, Md.

While Metchnikoff, Herter, and Kendall illustrated host resistance to probiotic bacteria, other researchers in the latter half of the 20th century determined that this resistance also can apply to pathogens. In 1956, Rolf Freter successfully established a streptomycin-resistant strain of Vibrio cholerae in antibiotic-treated mice and guinea pigs. Shortly thereafter, C. Phillip Miller, Marjorie Bonhoff, and David Rifkind postulated that indigenous microbes prevent infections, following experiments in which they used streptomycin to change the composition of the mouse microbiome. In 1965, Rose Mushin and Rene Dubos noted their inability to infect adult mice with enteropathogenic Escherichia coli, positing that mice develop “a microbiota which is antagonistic to E. coli.”

The term “colonization resistance” was coined in 1971, though usage of the synonymous phrase

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### Proposed Terminology

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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</thead>
<tbody>
<tr>
<td>Microbiome</td>
<td>A host-associated microorganism</td>
</tr>
<tr>
<td>Pathogen</td>
<td>A microbiont under conditions in which it causes disease</td>
</tr>
<tr>
<td>Mutualist</td>
<td>A microbiont under conditions in which it and its host provide mutual benefit</td>
</tr>
<tr>
<td>Commensal</td>
<td>A microbiont under conditions in which it neither provides benefit nor causes harm to its host while receiving some benefit from the association. The term has also been used to describe bacteria that are benign in some situations but detrimental to their hosts in others.</td>
</tr>
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</table>
“microbial interference” dates back to the late 1950s. Recent observations that germ-free mice are more susceptible to infection than normally colonized animals support the fundamental principle of colonization resistance, which can reflect the interactions of the indigenous microbiota with either the host immune system or the invading pathogens.

Several recent reviews explore the relationship between the microbiome and host function; here, we focus on the interplay between residents and invaders. Colonization resistance can result from either exploitative or interference competition between microbes. For instance, *E. coli* strain Nissle 1917 is a normal gut resident that limits *Salmonella Typhimurium* colonization in mice by competing for and sequestering iron, an example of exploitative competition.

*V. cholerae* colonization of the intestine illustrates interference competition, or direct antagonism between competitors. Several of its genes confer immunity to the type VI secretion system (T6SS) of other bacteria, enabling *V. cholerae* to defend against attack by members of the indigenous microbiota and thus to establish infection. Moreover, specific bacterial taxa inhibit *V. cholerae* colonization in humans, and recovery from *V. cholerae* infection involves recolonization by indigenous bacterial residents, suggesting that the roles of other community members in response to infection warrant further investigation.

**Resident Microbes Gone Rogue: Commensal-to-Pathogen Switching**

Although indigenous microbial communities can protect their hosts from invading pathogens, under certain conditions some of these community members can be detrimental to their hosts. The transition from the neutral to the detrimental role is referred to as the commensal-to-pathogen switch, and these community members are known as opportunistic pathogens or pathogens. Unlike pathobionts, “true” pathogens can produce intracellular infections, stimulate the host immune system, express virulence determinants, and infect healthy hosts.

The commensal-to-pathogen switch can follow an active change in behavior, but is more often associated with either passive translocation of a microorganism to a different host tissue or to host-created changes in its environment. For example, as a gut resident, *Bacteroides thetaiotaomicron* benefits the host by stimulating immune development and fermenting carbohydrates. Yet, when it is translocated from the gut, *B. thetaiotaomicron* infects tissues in the brain, liver, pelvis, and lungs. Similarly, *B. fragilis* strains are benign in the human intestine, but cause very serious infections in the bloodstream and are recovered from up to 30% of abdominal infections. Other gut residents such as *Clostridium sordellii* and extraintestinal pathogenic *E. coli* (ExPEC) escape the gut to colonize distal sites and disrupt host homeostasis.

The ability to cause disease following translocation to a new site in the host is not limited to intestinal microbes. *Streptococcus pneumoniae* is an innocuous resident of the upper respiratory tract, where it outcompetes other members of the microbiota, including *Haemophilus influenzae*, by producing bactericidal hydrogen peroxide. However, at other sites, it expresses a pore-forming toxin that damages host tissues in the middle ear, lung, and bloodstream, causing disease. Similarly, *Staphylococcus aureus*, an ordinary member of the skin consortia in up to 25% of the population, is frequently pathogenic when it enters the blood, causing pneumonia, abscesses, and systemic sepsis such as toxic shock syndrome.

Changes in human physiology that alter microbial habitats also can potentiate the commensal-to-pathogen switch. For example, when the skin is exposed to elevated temperatures and humidity, endogenous corynebacteria can cause several skin diseases, including pitted keratolysis, trichobacteriosis, and erythrasma. Similarly, suppression of the host immune response encourages *Streptococcus mitis* to shift from being a harmless member of the oral microbiota to a virulent pathogen that causes endocarditis, bacteremia, and septicemia.

Meanwhile, chronic stress in animals induces them to produce catecholamines, which bind iron, removing it from the host iron-binding proteins, transferrin and lactoferrin, and thus making it available for *E. coli* to use in causing infections. Since mammalian hosts limit iron to suppress pathogens, their producing catecholamine hormones proves self-destructive for those hosts when it is exploited by pathogens. This dynamic interplay between commensal microorganisms and their hosts regulates the spatial dis-
Dysbiosis, Colonization Resistance, and the Commensal-to-Pathogen Switch

Although microorganisms in host-associated ecosystems adapt readily to minor environmental changes, extreme changes may challenge the entire community and lead to substantial consequences for the host. Perturbing the microbiota can cause dysbiosis—that is, changes that so disrupt the structure of a microbial community that they impair critical functions, including its ability to resist invading microorganisms. Dysbiosis can manifest itself in changes of community structure, metagenome structure, or gene expression.

Enterococcus infection provides a clinically important system for understanding the relationship between dysbiosis and commensal-to-pathogen switching. Enterococcus spp. can induce pelvic, neonatal, and urinary tract infections. In immunocompromised stem cell transplant patients, overgrowth of vancomycin-resistant enterococci (VRE) in the intestine precedes bloodstream infection. In these disrupted gut communities, populations of lactobacilli and related taxa are replaced by clostridia, enterococci, and members of the Enterobacteriaceae family. These changes in the microbiota can withstand antibiotic treatment, leading to persistent infections. However, fecal transplants containing a Barnesiella species cure these infections in some patients, suggesting that changes in the gut community accompany VRE invasion, domination, and infection.

Although the well-documented association between antibiotic treatment and Enterococcus infection suggests that the gut community plays a role in Enterococcus infection or its prevention, the community’s role in commensal-to-pathogen switching during Enterococcus infection is unknown. In the insect Manduca sexta, the loss of gut integrity enables E. faecalis to translocate to the hemolymph, where it induces hemocyte aggregation and host death due to sepsis. Similarly, in mice treated with antibiotics and irradiated to deplete macrophages, E. faecalis migrates to the mesenteric lymph nodes from which it induces sepsis, consistent with a commensal-to-pathogen switch.

These findings support the idea that disrupting the gut community reduces its resistance to being colonized and enables commensal bacteria to become pathogens. The results also suggest that the microbiota has a dual protective role—modulating host immunity and outcompeting Enterococcus populations. Studying Enterococcus in both insects and mammals provides complementary insights. In insects, the role of the innate immune system can be studied in the absence of adaptive immunity and the gut community is simple, whereas studies in mice probe a more complex immunological response involving a more highly diverse gut microbial community. The well-studied case of Enterococcus commensal-to-pathogen switching provides a foundation for the study of other pathogens.

Conclusions

Following the application of Koch’s postulates to identify genetic determinants of virulence, an immense research effort has helped to elucidate how host and microbial factors contribute to infections. However, many of those studies focused primarily on binary interactions between hosts and exogenous pathogens while ignoring host-associated microbial communities. This narrow
focus simplified the problem, making it approachable with 20th-century analytics.

Recent advances, however, make it possible to address infectious disease as a more complex system involving many additional factors. To determine the role of communities in disease, many familiar models of pathogenesis need to be amended to accommodate the microbiome. Future inquiry should include comprehensive assessment of the structure and function of microbial communities at all stages of infection, while also defining community and metagenome changes that antibiotic treatments induce. Likewise, the impact of the microbial community on host, pathogen, and disease outcomes should be considered an essential aspect of infectious disease.

Disease management based on ecology of the human microbiome is still in its infancy. Deliberately manipulating microbial communities will require an understanding of genetic and molecular factors that modulate community stability and vulnerability. Such research will depend on us learning which members of the microbial community play clear roles during infections, as well as how their absence and the loss of their metabolic capacities affect those infections. Integrating genomic and metabolomics data with classical genetic analysis will also provide critical insights into the role of the resident community as a barrier to and source of infectious agents in the human ecosystem.

Jessica Miles is a Ph.D. candidate and Jo Handelsman is the Howard Hughes Medical Institute Professor and Frederick Phineas Rose Professor in the Department of Molecular, Cellular and Developmental Biology, Yale University, New Haven, Conn.; Jonathan F. Holt is a Lecturer in the Biological Sciences Department, Edgewood College, Madison, Wis.

Suggested Reading


Novel Rifamycin Analogs to Treat Multidrug-Resistant Tuberculosis

Amycolatopsis mediterranei, which makes rifamycin B, can be engineered to produce analogs that inhibit rifamycin-resistant strains of M. tuberculosis

Shannon Weiman

Emergent multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains of Mycobacterium tuberculosis are causing a crisis in efforts to treat patients with tuberculosis (TB). Such infections are highly lethal and on the rise, particularly in developing nations. In some cases, a single strain carries resistance to all available drugs for treating this pathogen.

Rup Lal of the University of Delhi dedicated 25 years of research to generating novel antibiotic candidates against TB, persevering through setbacks and disappointments. These efforts culminated in synthesis of novel rifamycin B analogs. A semisynthetic derivative of this analog is more potent than currently available drugs, including drug-resistant TB strains, he says. Meanwhile, his research group’s approach, which is based on genetic engineering to generate such analogs, is itself something of a breakthrough, one that will enable Lal and his collaborators to produce and evaluate many additional antimicrobial candidates in the future.

Drug-Resistant TB, a Crisis within the Global Tuberculosis Epidemic

TB is the second-leading cause of death worldwide due to a single infectious agent, second only to HIV/AIDS. TB is also responsible for 25% of HIV-related deaths, according to the World Health Organization (WHO). The death toll from TB in 2013 tallied 1.5 million, while 9 million individuals are infected globally.

Several classes of antibiotics are used to treat TB—typically, with drugs of several types used in combination. All these regimens are administered to patients for prolonged periods lasting from 6 months to 2 years, making it difficult for many individuals to complete. Poor adherence to these regimens, particularly for individuals living in developing nations where drug access can be challenging, contributes to rampant drug resistance among M. tuberculosis strains. “Drug-resistant TB is the manmade result of interrupted, erratic, or inadequate TB therapy, and its spread is undermining efforts to control the global TB epidemic,” notes the TB Alliance, a global nonprofit organization with offices in New York, Brussels, and Pretoria.

MDR TB, defined by resistance to both first-line antibiotics rifamycin and isoniazid, is a growing concern. Since its emergence in the 1980s, the number of MDR cases increased steadily, reaching an estimated 480,000 cases in 2013, according to WHO. In some regions, MDR-TB accounts for up to 20–30% of all TB cases.

Resistance against second-line treatments is also becoming more common, leaving patients...
and physicians with fewer and fewer options. These XDR strains, which are resistant to first- and second-line drugs, account for 9% of TB cases and are reported as occurring in more than 100 countries, according to WHO. Some totally resistant strains (TDR), which do not respond to any available antibiotics, are also being documented, officials note.

“TB has been a rampant health threat worldwide, and is most devastating in underdeveloped and developing countries,” Lal says. “It has been so for the last several decades, and the situation is worsening with the emergence of MDR and TDR strains. To combat this situation new rifamycin analogs are needed, as the drugs used currently are ineffective against these resistant strains.”

Resistance Developed to Rifamycin and Several Analogs Critical for Treating TB

Rifamycins are semisynthetic derivatives of the natural product rifamycin B, which is produced by the soil actinobacterium *Amycolatopsis mediterranei*. While rifamycin B itself has moderate antimicrobial activity, various semisynthetic analogs have improved potency as well as other properties that make them better drugs for treating TB. Discovered in the 1950s, rifamycins became a mainstay of TB treatment in the 1960s, significantly improving patient survival rates. However, resistance soon emerged as mutations in *M. tuberculosis* led to poorer binding of rifamycin to its target and, hence, reduced susceptibility.

Rifamycins target the bacterial RNA polymerase enzyme, blocking RNA chain elongation and downstream protein synthesis, which is essential for bacterial survival. Dozens of escape mutations have been described in clinical isolates of rifamycin-resistant *M. tuberculosis*, nearly all of them within an 81-bp region of the RNA polymerase gene. The vast majority of these alter at least one of three key codons that mediate interactions of the encoded enzyme with rifamycins.

One major approach to overcoming resistance to this and other antibiotics is to generate structural analogs of the parent antibiotic, allowing the analogs to circumvent the mutations that render the parent drugs inactive. However, rifamycin presents medicinal chemists with challenges that they could not readily surmount. The complicated structure of rifamycins makes them difficult to synthesize or to modify. “Structural complexity of rifamycin B limits the use of chemical tools to generate fundamentally different rifamycin analogs, such as modification of the backbone structure,” Lal says. “Only the napthoquinone ring is sterically available for chemical modifications, while the rest of the chain is not amenable.”

In practice, chemists succeeded in producing only four clinically useful analogs of rifamycin B: rifampicin, rifaximin, rifabutin, and rifapentine, all modified on the C-3 or C-4 position of the naphthalene moiety. Resistance developed against all of them.

Genetically Engineering for the Biosynthesis of Novel Rifamycin Analogs

Despite these difficulties, medicinal chemists continued trying to generate additional rifamycin analogs but to no avail, according to Lal. “Further modification to produce effective analogs seemed untenable,” he says. Those failures from conventional efforts to generate additional analogs of rifamycin led Lal and his team to take a different approach. Setting aside organic chemistry for the moment, they turned instead to the microorganism that makes rifamycin B to see whether it could be changed to synthesize novel analogs of that natural product. Their strategy was to engineer *A. mediterranei* by modifying genes that encode some of the enzymes that synthesize rifamycin B. These changes then could yield novel structures that retain activity against *M. tuberculosis* but overcome resistance to older, semisynthetic members of this family of antibiotics.

This same approach was used to generate novel analogs of other antibiotics, including erythromycin and rapamycin. In both those cases, biosynthetic gene clusters within their respective producer strains, *Saccharopolyspora erythraea* and *Streptomyces hygroscopicus*, yielded novel analogs. Further, in both those cases and in the case of rifamycin B, key enzymes belong to the type I polyketide synthase (PKS) family, according to Lal.

“Type I PKSs, such as *ery*PKS, have been shown to be amendable to combinatorial biosynthetic modifications to give new analogs of antibiotics,” he says. “The genetic organization of the modules in the rifamycin biosynthetic pathway is collinear, similar to the erythromycin and rapamycin PKSs. This collinear architecture makes it a possible target for combinatorial biosynthesis.”

However, the approach was still a gamble. Other microbial PKS systems are difficult to
engineer due to the sheer number of genes and enzymatic modules involved. Additionally, downstream enzymes may not recognize or act on modified substrates being produced within genetically altered strains.

The biosynthetic gene cluster for rifamycin B contains dozens of genes, many with multiple enzymatic modules. These modules add various sidechains to intermediates along the pathway leading to rifamycin or rearrange the overall structure of specific intermediates. For example, starting with the relatively simple precursor molecule dihydroxybenzoic acid (AHBA), the rifA through rifE genes elongate its carbon backbone prior to cyclizing those downstream intermediates to close the polyketide ring.

Lal set his sights on modifying rifB, which encodes three acetyltransferase modules, each of which adds a 3-carbon propionate to the elongating chain. Through genetic recombination, Lal replaced one of these modules with an acetyltransferase-encoding module within a gene plucked from the rapamycin biosynthetic pathway, which instead adds 2-carbon acetate. This modification removes a carbon from the backbone at the C-24 position, which directly interacts with the target RNA polymerase. The final product following this specific modification in the pathway is 24-desmethylrifamycin B, a rifamycin analog that had never been made before, according to Lal. “This work focuses on the design strategy that gains access to rifamycin analogs in which modifications take place in the polyketide backbone,” he says. Other analogs made via medicinal chemistry before then were restricted to changes to the C-3 and C-4 of the naphthalene ring.

“It is conceivable that this is the most elegant of manipulations that have been done,” says David Rothstein, an industry consultant based near Boston, who worked on developing rifamycin analogs throughout much of his career. “It is quite elegant to put the module of one enzyme into another complex that is carrying out this reaction.”

**This Strategy for Modifying Rifamycin Took Decades To Implement**

Although an elegant concept, however, genetically manipulating *A. mediterranei*, proved far more difficult to implement than Lal anticipated.

**ASM Fellowship Program Enabled Lal To Continue Pursuing His Strategy**

In 2009 Lal applied for and received an ASM Indo-US Professorship, which provides funding for microbiology research that forges new collaborations between scientists in India and the United States. Lal teamed up with Taifo Mahmud of Oregon State University, an expert in bioengineering and natural product chemistry, to analyze more than 100 candidate bacterial clones for production of the new rifamycin analog.

The program, sponsored by the Indo-US Science and Technology Forum (IUSSTF) and managed by ASM, began in 2003. During its first decade, the program supported 59 professorship grants resulting in long-term collaborations through research grants and dissemination of expertise to hundreds of students through teaching professorships. A few years ago, ASM and IUSSTF signed an extended partnership agreement to guarantee $75,000 in funding to fellows who implement projects between 2014 and 2016. The program now awards four to five Teaching and/or Research Professorships per year, and each award is for $5,000.

Lal also worked with Yogendra Singh, recipient of the ASM Moselio Schaechter Distinguished Service Award (2013–14), at the Institute of Genomics and Integrative Biology (CSIR-IGIB), Delhi, to test some of the new compounds. He continues to work with Mahmud, further developing the relationship they forged under the ASM Indo-US Fellowship. Together they have procured funding from the Indian government’s Department of Biotechnology to generate additional analogs of rifamycin B—work that may not have been possible without ASM support back in 2009.

Lal has also become more involved with ASM, joining the International Education Committee and taking on a leadership role as the ASM ambassador to the Indian Ocean region as of 2012. “As an ambassador I have conducted around 19 ASM workshops to promote microbiology in India and enrolled around 800 ASM members,” he says. During his tenue Lal has also formed an International Student Chapter in India, and initiated a collaboration between the ASM and the Association of Microbiologists of India (AMI). “Every year at the national AMI conference, an ASM conference and joint AMI-ASM session is conducted to foster collaborations between these two societies,” he says.

He and his collaborators spent more than 25 years to make the project work, dealing with numerous challenges and interim failures along the way.

Lal and his wife Sukanya Lal began trying to manipulate the genes of *A. mediterranei* as post-doctoral fellows in Germany in 1988. During that early stage, it took them about a decade to develop and optimize cloning vectors and transformation protocols. Those efforts continued after
they returned to India, where he took a faculty position at the University of Delhi, and she joined Ramjas College at the same university, where she continues teaching undergraduate students. Moreover, Lal could not bring these genetic tools to bear on the rifamycin biosynthetic gene cluster prior to 1998 because those genes were still being characterized. Thus, it took another 15 years to accomplish the next steps of putting those tools to use.

Low transformation efficiencies and homologous recombination rates made for slow progress, with plenty of negative and false-positive results as well as funding challenges to confront. Despite these challenges and setbacks, Lal and his team persevered, motivated by the importance of their work to global health and for their homeland in particular. “TB claims 1 million lives per year globally, and 20–25% of these deaths are from India alone,” he says. Many MDR, XDR, and TDR strains, which have high mortality rates, circulate in India, he points out. “It was my stu-

Other Candidate Compounds with Activity against MDR-TB

Other research groups are seeking compounds with activity against multidrug-resistant (MDR) strains of *Mycobacterium tuberculosis*, including:

- One novel compound that also inhibits mycobacterial RNA polymerase, but is distinct from rifamycin, binds to the polymerase about 18 Å from the rifamycin binding site, making it effective against rifamycin-resistant MDR-TB strains, according to Vasu Nair and his colleagues at the University of Georgia, Athens. Further, it synergizes with PA-824, which inhibits *M. tuberculosis* cell wall synthesis, making a potent anti-MDR-TB cocktail. “The combination improved the MIC of compound 2 by eightfold, and that of PA-824 by fourfold,” he says.

- To circumvent resistance to isoniazid, another first-line treatment for TB, Ujjini Manjunatha at the Novartis Institute for Tropical Disease in Singapore and his collaborators are seeking direct inhibitors of the cell wall-synthesis enzyme. Isoniazid is a prodrg that depends on the enzyme encoded by KatG for activity, but mutations in this gene render it inactive against that enzyme. “Over the last two decades, efforts have yielded many potent structurally diverse direct InhA inhibitors, but so far with limited success in achieving an orally active candidate,” he says. However, a new class of compounds, the 4-hydroxy-2-pyridones, shows great promise. One of them, NITD-916, is five to eight times more potent than isoniazid itself, even against drug-resistant TB strains. “We propose that binding of 4-hydroxy-2-pyridones to the InhA-NADH complex inhibits the fatty acid elongation step, resulting in blocking the biosynthesis of mycolic acids, weakening of the cell wall... and ultimately lysing Mtb,” he says.

- Pretomanid, a nitroimidazole, belongs to a class of antibacterial agents with a novel mechanism of action against *M. tuberculosis*, according to the TB Alliance. This drug candidate, one of many being studied by the Alliance, is active in vitro against drug-resistant clinical isolates, and is a potent bactericidal agent when tested in mice. Moreover, it shows no significant cytochrome P450 interactions, and no significant activity against a broad range of gram-positive and gram-negative bacteria.

- Sirturo (Bedaquiline) a new drug for treating drug resistant tuberculosis was developed by Janssen, a part of Johnson & Johnson. In late 2012 it became the first new drug for TB to be approved by the Food and Drug Administration in 40 years. Its use is restricted to patients with MDR-TB. This novel orally administered TB drug is a diarylquinoline that inhibits mycobacterial ATP synthase but has no significant effect on ATP levels in human mitochondria.

- The diamine SQ109 is active against drug-resistant clinical strains, and shows synergistic activity with the first-line drugs rifampicin and isoniazid in vitro and in vivo. according to Sequella in Rockville, Md. It is in a phase 2/3 pivotal trial in Russia. Meanwhile, SQ609, which contains a dipiperidine pharmacophore and targets the cell wall of this bacterial pathogen, shows additive or synergistic activity with all of the first-line TB drugs. Sequella also is developing Sutezolid, an oxazolidinone. Safe and well-tolerated, it showed significant early bactericidal activity and potential efficacy during a phase 2 clinical trial.

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Facing Further Challenges while Generating and Evaluating Rifamycin Analogs

In 2009, seeking support to continue this research, Lal applied for and received an ASM Indo-US Professorship (see box, p. 377). He also teamed up with Taifo Mahmud of Oregon State University, who is an expert in bioengineering and natural product chemistry, to analyze more than 100 candidate bacterial clones that were intended to produce rifamycin analogs.

“To our utter dismay, we found out that all the mutants that we had generated produced only rifamycin B and not the expected (novel) compound,” Lal recalls. Still they did not give up. “Although it was a very frustrating experience, we discussed how to proceed further and got a new strain of *Amycolatopsis mediterranei* S699 from Taifo Mahmud that had some additional features to make our selection of mutants more accurate and easy.”

This strain made a huge difference and, in 2011, Lal and his collaborators at last struck gold, he says. Aeshna Nigam, one of Lal’s graduate students, generated fresh mutants that again were sent to Mahmud for analysis. Three strains in this new set produced the long-sought novel rifamycin analog, 24-desmethylrifamycin B. The expertise of Mahmud and his group proved critical, Lal says.

This biochemical success was worth celebrating on its own, but whether the novel analog had any antimicrobial activity was yet to be determined. Even if it did, it might not be effective against drug-resistant strains of *M. tuberculosis*. Many MDR-TB strains are cross-resistant against multiple rifamycin analogs because escape mutations tend to allow RNA polymerase to evade structural similarities across this class of antibiotics.

To evaluate the activity of the new compound, Lal turned to his collaborator Yogendra Singh, recipient of the 2013 ASM Moselio Schaechter Distinguished Service Award (see box, p. 377), at the Institute of Genomics and Integrative Biology (CSIR-IGIB), Delhi. After converting the bacterial product into its semisynthetic derivative, 24-desethylrifamycin B, the novel analog performed in vitro comparably to, or better than, several clinically used members of the rifampicin family of antibiotics against various pathogenic bacteria, including *Staphylococcus aureus, M. tuberculosis*, and even rifampicin-resistant *M. tuberculosis* strains, according to Singh and his collaborators.

“While we anticipated that altering the functional group at this particular position would be directly associated with the change in the antibiotic potential, we were not very sure if the analog would be biologically effective or not, and the work with CSIR-IGIB helped us in proving its effectiveness,” Lal says. “Its better antibiotic potential has been a fortunate discovery.” He postulates that the activity against rifampicin-resistant strains may be due to increased flexibility of the demethylated compound, allowing it to bind to mutated RNA polymerases while older analogs of rifampicin cannot. The analog might be further improved by chemically modifying its C-3 and C-4 positions, he adds.

Resistance Possibilities Loom Even for Novel Analogs

The success of these new compounds could be short-lived, warns Rothstein. Resistance tends to develop quickly against rifamycin antibiotics because of the abundance of RNA polymerase escape mutations, he says.

Lal agrees and anticipates producing many different novel analogs with which to keep ahead of such resistance. “Now with the proof of concept in hand we are trying to develop a library of rifamycin analogs, with modifications targeted at other domains and modules of the rifamycin PKS gene cluster,” he says. “The combined genetic and synthetic approach holds great potential to generate a wide variety of rifamycin analogs that may be effective against the global threat of MDR-TB... and other life-threatening pathogens.”

“This [technique] is a real breakthrough,” says Rothstein. “That’s not to say that the compounds produced will be necessarily better. That has to be tested. It’s a roulette wheel if what comes out will be any better.” New analogs might have improved—or worse—toxicity profiles or fewer drug-drug interactions, which could give them an edge in or keep them out of the clinic. Rifamycins are notorious for inducing cytochrome P450 drug-metabolizing enzymes, which degrade other drugs and undermines overall efficacy in
treating TB patients, especially those who are also being treated for HIV/AIDS. A novel rifamycin analog without these issues would be ideal for clinical development.

Lal’s approach might also be applied more broadly to generate analogs of other antibiotics, as has been done with erythromycin and rapamycin. However, Lal warns that the lengthy process of developing tools for genetically engineering antibiotic-producing microbial species can be cumbersome. “It would require extensive standardization of protocols as the technique is organism- and antibiotic-specific,” he says. “Despite these limitations, the scope of diversifying natural products through mechanisms as this is endless. Misadventures with strong lessons . . . are not failures [but] part of the march to success.”

Shannon Weiman is a freelance writer in San Francisco, Calif.

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ASM Announces Senior Editors for mSphere™ and mSystems™

The launch of ASM’s two new interdisciplinary open-access journals, mSphere and mSystems, is scheduled for early 2016. mSphere is a pan-microbiology journal that will publish high-quality research by scientists whose work falls outside the scopes of traditional ASM specialty journals. mSystems is a systems microbiology journal that will publish cutting-edge, significant advances in research associated with metabolic and regulatory systems on the scale of both a single cell and entire microbial communities. Both journals will provide streamlined decisions along with short publication times, to ensure important findings are available to the scientific community as quickly as possible.

Formal Calls for Papers are scheduled for September 2015. Visit msphere.asm.org and msystems.asm.org for more information.

ASM is pleased to announce the appointment of Senior Editors for mSphere and mSystems effective 1 July 2015.

Editor in Chief Michael Imperiale
Appoints mSphere™ Senior Editors

**Ira Blader**, Ph.D., is an Associate Professor at SUNY Buffalo’s Department of Microbiology and Immunology. His research team is focused on identifying how transcription factors function and how the parasite adapts to the various oxygen environments it encounters during its life cycle. Additionally, the team is exploring our understanding of how *Toxoplasma* causes ocular disease by developing a murine ocular toxoplasmosis model to identify parasite virulence factors and to study immune responses in the eye. Blader previously served as an Associate Professor at the University of Oklahoma Health Science Center. He is currently a panel member of the NIH Pathogenic Eukaryotes Study Section.

**Melanie Blokesch**, Ph.D., is the head of the Laboratory of Molecular Microbiology at the Swiss Federal Institute of Technology in Lausanne (EPFL), Switzerland. Her research primarily focuses on how bacteria evolve in natural environments to emerge as human pathogens and how horizontal gene transfer contributes to pathogen emergence. The model organism for these studies is the causative agent of cholera, *Vibrio cholerae*. Recent work by the Blokesch group deciphered new aspects of the regulatory network that governs natural competence for transformation, which is a widespread mode of horizontal gene transfer in bacteria. Moreover, cellular microbiology-based approaches used by her group provided important new insights into the mechanistic aspects of the DNA uptake process and the link between interbacterial competition (mediated via the type VI secretion system) and DNA transfer in *V. cholerae*. Blokesch holds a Ph.D. degree from the Ludwig-Maximilians-University in Munich, Germany. From 2005 to 2009 she worked as a postdoctoral fellow in the Division of Infectious Diseases and Geographic Medicine and the Department of Microbiology and Immunology of Stanford University. In 2009, she was appointed as tenure-track assistant professor within the School of Life Sciences at the Swiss Federal Institute of Technology in Lausanne, Switzerland.

**Patricia Bradford**, Ph.D., is the Executive Director of Infectious Disease Research at AstraZeneca Pharmaceuticals, where she also serves as the Head of Development Microbiology. In her current position, Bradford supports the Phase 3 and registration efforts for late stage β-lactam
products. Previously, she led biology efforts on discovery platforms for antibiotics and antivirals as the company’s Head of Biology. As the Director of Infectious Disease at Novartis, Bradford managed a diverse group of scientists with specialties in clinical microbiology, in vivo pharmacology, biochemistry, and bioinformatics.

Carolyn Coyne, Ph.D., is an Associate Professor at the University of Pittsburgh’s Department of Microbiology & Molecular Genetics. She is also the principal investigator at the Coyne Lab, which focuses on (1) the mechanisms by which enteroviruses have evolved to successfully circumnavigate the barriers presented by polarized cells to facilitate virus entry, replication, and spread, (2) the mechanisms utilized by enteroviruses to evade and/or suppress innate immune signaling, (3) the identification of novel regulators and components of the innate immune system, and (4) the role of placental-specific microRNAs in antiviral signaling and the induction of autophagy at the maternal-fetal interface. Coyne is a member of Faculty of 1000 (Virology), serves on the editorial boards of the Journal of Virology® and Virology, and as is an associate editor of PLoS Pathogens.

Sarah D’Orazio, Ph.D., is an Associate Professor in the Department of Microbiology, Immunology, and Molecular Genetics at the College of Medicine. D’Orazio’s dissertation work at the University of Miami School of Medicine focused on Bacterial Pathogenesis, and she did a postdoctoral fellowship in Immunology at Harvard Medical School. Research in her lab focuses on understanding the complex interplay between the virulence strategies of the bacterial pathogen Listeria monocytogenes and the immune defense mechanisms of the host. Her lab uses a mouse model of foodborne infection to study how the balance of these factors results in a wide spectrum of human disease, ranging from mild, self-limiting gastroenteritis to life-threatening systemic infections that can invade both the brain and the placenta. D’Orazio received her Ph.D. in Microbiology & Immunology from the University of Miami School of Medicine.

Paul Duprex, Ph.D., is an Associate Professor of Microbiology at Boston University’s School of Medicine. He is also the Director of Cell and Tissue Imaging at the National Emerging Infectious Diseases Laboratories Institute in Boston. His research involves understanding the molecular basis of pathogenesis and attenuation of respiratory paramyxoviruses, with the aim of developing rationally attenuated vaccines for these viruses. Duprex serves as an editor for FEMS Microbiological Reviews, Journal of General Virology, and PLoS Pathogens. He received his Ph.D. from The Queen’s University of Belfast.

Katherine McMahon, Ph.D., is a Professor at the University of Wisconsin, Madison, in the Departments of Civil & Environmental Engineering and Bacteriology. McMahon’s lab studies the microbial ecology of both natural and engineered systems using molecular tools to investigate microbial community structure and function in lakes and activated sludge. Her team uses molecular tools to investigate microbial community composition, dynamics, and function, while integrating principles of ecology and engineering to explain observed patterns. McMahon received her Ph.D. from the University of California, Berkeley.

Aaron Mitchell, Ph.D., is a Professor at the Department of Biological Sciences at Carnegie Mellon University. His research focuses on Candida albicans, with the objective of defining the determinants of pathogenicity and drug responses in order to identify strategies to improve diagnosis and therapeutics. Mitchell’s work has two goals: (1) to define the regulatory pathways and signals that promote biofilm formation, and to understand the steps in biofilm development that they control, and (2) to determine how regulatory pathways are rewired during infection, and what the ultimate outputs may be that permit growth in the infection environment. Mitchell has served as Editor in Chief of Eukaryotic Cell® since 2010. He is also an associate editor for PLoS Pathogens, a section editor for
Susannah Tringe, Ph.D., is head of the Metagenome Program at the Department of Energy Joint Genome Institute, where she oversees research using DNA sequence data to study communities of microbes from diverse environmental niches. Her major research interests relate to microbial influences on greenhouse gas uptake and release in wetlands and how microbes interact with plants to affect growth, health, and disease resistance. Tringe received her undergraduate degree in Physics from Harvard University then went on to a Ph.D. in Biophysics from Stanford University. From there she spent a few years in a yeast genetics lab at the University of New Mexico before joining Edward Rubin’s group at Berkeley Lab as a postdoc in 2003. There she developed techniques for using DNA sequence data for comparative analysis of whole microbial communities, rather than individual organisms, a field now known as metagenomics. In 2011 she was awarded an Early Career Research grant from the Department of Energy to study microbial communities in wetlands and the potential for wetland restoration to serve as an effective carbon sink.

Pieter Dorrestein, Ph.D., is a Professor at the Skaggs School of Pharmacy and Pharmaceutical Sciences in the Departments of Pharmacology, Chemistry and Biochemistry at the University of California, San Diego. He also heads the Dorrestein laboratory, which aims to develop new mass spectrometry approaches to detect and characterize therapeutic leads as well as their biosynthesis. The research in his lab falls into four areas: (1) The functional characterization of novel post translational modifications involved in the biosynthesis of therapeutics or therapeutic targets. (2) Development of new methods to characterize metabolic exchange factors from microbial systems involved in cell-to-cell communication. All cells communicate with other cells. Currently, there are no tools to systematically study the molecular output of a small population of cells. Dorrestein’s lab is developing mass spectrometry based approaches to study the universal phenomenon of cell-to-cell communication to discover new biological modulators. (3) Therapeutic target identification, including off-targets. Target identification is very important to the therapeutic discovery pipeline. This is done in collaboration with other scientists at UCSD, UCSC, SALK, SIO and elsewhere. (4) Monitoring the global response of therapeutics by monitoring the signaling proteome. While a therapeutic may have one or a few targets, the entire proteome of a cell or tissue will be affected. The phosphoproteome provides insight into the effect therapeutics have on cells or tissues and is monitored upon therapeutic stimulation providing insights into key regulatory pathways. Dorrestein received his Ph.D. from the University of Illinois, Urbana-Champaign.
Jonathan Eisen, Ph.D., is a Professor at the University of California, Davis, with appointments in the School of Medicine and the College of Biological Sciences. His research focuses on communities of microbes and how they provide new functions—to each other or to a host. His study systems have included boiling acid pools, surface ocean waters, agents of many diseases, and the microbial ecosystems in and on plants and animals. He is also coordinating the largest microbial sequencing project to date—a Genomic Encyclopedia—being done at the DOE Joint Genome Institute, where he holds an Adjunct Appointment. His overarching goal in his research is to create a “Field Guide to the Microbes.” Prior to UC Davis, he was on the faculty of The Institute for Genomic Research and held an Adjunct Appointment at the Johns Hopkins University. Eisen is the Academic Editor in Chief of PLoS Biology. Eisen received his Ph.D. from Stanford University.

Julie Huber, Ph.D., is an Associate Professor of Ecology and Evolutionary Biology at Brown University and the Associate Director of the Josephine Bay Paul Center’s Marine Biological Laboratory. She is a microbial oceanographer by training and is broadly interested in microbial ecology and understanding how microbial communities establish, function, and evolve in diverse ecosystems. Her research program investigates deep-sea microbial ecosystems with an emphasis on using crustal fluids to interrogate the rocky subseaﬂoors habitat. Huber is funded by a variety of agencies, including the NSF, NASA, the Gordon and Betty Moore Foundation, and the Alfred P. Sloan Foundation’s Deep Carbon Observatory. In 2007, she received the L’Oreal USA Fellowship for Women in Science. Huber received her Ph.D. from the University of Washington.

Janet Jansson, Ph.D., is the Division Director of Biological Sciences at the Paciﬁc Northwest National Laboratory (PNNL). She obtained her Ph.D. in 1988 at Michigan State University and then established a successful research career in Sweden over the next 20 years. From 2000 to 2006, she was the Professor and Chair of Environmental Microbiology at the Swedish University of Agricultural Sciences and Vice Dean of the Natural Sciences Faculty, where she coordinated the Swedish strategic national center of excellence, the Uppsala Microbiomics Center. From 2007 to 2013, she was a senior staff scientist at Lawrence Berkeley National Laboratory and from 2012 to 2014 an Adjunct Professor at UC Berkeley and the University of Copenhagen. She was recruited to PNNL in June 2014, and she currently also serves as the President of the International Society for Microbiology (ISME) and as a senior editor of the ISME Journal. Jansson has more than 30 years’ experience in microbial ecology, with speciﬁc expertise in the use of molecular approaches (omics) to study complex microbial communities, such as those residing in soil, sediments, and the human gut. She is a Fellow of the American Academy of Microbiology, has more than 110 publications, and is the editor of two books on molecular microbial ecology and one textbook on soil microbiology.

Rob Knight, Ph.D., is a Professor at the University of California San Diego’s Departments of Pediatrics and Computer Science & Engineering. He completed a B.Sc. in Biochemistry in his native New Zealand at the University of Otago, then completed a Ph.D. on the origin and evolution of the genetic code with Laura Landweber in the Department of Ecology and Evolutionary Biology at Princeton University. He conducted postdoctoral research with Mike Yarus on RNA sequence space in the Department of Molecular, Cellular and Developmental Biology at the University of Colorado, and then was the first hire in the interdisciplinary BioFrontiers Institute (then CIMB) at the University of Colorado in 2004. Much of Knight’s research focuses on the microbiome. He has participated in discoveries including linking gut microbes to obesity, to diet, to geography, to age, and to host behavior; the individualized nature of our microbes, which even link us to objects we touch; the role of pH rather than plant community or biome in structuring soil microbial communities globally; and the deep microbial ”seed bank” that occurs in marine and perhaps other ecosystems. In 2009 he became an HHMI Early Career Scientist, and in 2012 he became an AAAS Fellow.
Margaret McFall-Ngai, Ph. D., is currently Director of the Pacific Biosciences Research Center (PBRC) at the University of Hawaii at Manoa and a Professor at PBRC’s Kewalo Marine Laboratory. Her laboratory studies the role of beneficial bacteria in health using the squid-vibrio model and the biochemical and molecular “design” of tissues that interact with light. In addition, she has been heavily involved in promoting microbiology as the cornerstone of the field of biology. McFall-Ngai also currently holds emeritus status at the University of Wisconsin-Madison and the positions of Andrew D. White Professor-at-Large at Cornell University and EU Marie Curie ITN Professor. She was recently (2011 to 2013) a Moore Scholar at the California Institute of Technology. She has been a Guggenheim Fellow and is a member of the American Academy of Microbiology (2002), the American Academy of Arts and Sciences (2011), and the National Academy of Sciences (2014).

Katherine Pollard, Ph.D., is a Senior Investigator at the Gladstone Institutes. She is the founder and faculty supervisor of the Gladstone Bioinformatics Core and a Professor in the Department of Epidemiology and Biostatistics, Institute for Human Genetics, and Institute for Computational Health Sciences at the University of California, San Francisco (UCSF). Her lab develops statistical and computational methods for the analysis of massive genomic data sets. Her current projects focus on two major areas of genome evolution: identifying the genetic basis for human-specific traits, such as our susceptibility to AIDS and atherosclerosis, and characterizing the human microbiome through metagenomic data. She was previously an assistant professor at the University of California, Davis Genome Center and Department of Statistics. She was awarded the Thomas J. Watson Fellowship in 1995 and the Sloan Research Fellowship in 2008. She is also a member of the California Academy of Sciences. Pollard earned her master’s degree and Ph.D. in biostatistics from the University of California, Berkeley, where she developed computationally intensive statistical methods for the analysis of microarray data with applications in cancer biology. She implemented these approaches in Bioconductor, an open source software program used with high-throughput genomic data. As a comparative genomics postdoctoral fellow at the University of California, Santa Cruz, she participated in the Chimpanzee Genome Project and used this sequence to identify the fastest-evolving regions in the human genome, known as human accelerated regions.

Jeroen Raes, Ph.D., is a Professor at the Department of Microbiology and Immunology at Katholieke Universiteit Leuven. After his master’s in Biochemistry and master’s in Bioinformatics, Raes received his Ph.D. in bioinformatics and comparative genomics in the lab of Pierre Rouze and Yves Van de Peer from the University of Ghent. His focus was on the role of gene and genome duplication in evolution and the birth of novel gene functions. After an IWT postdoc with CropDesign on the identification of novel yield target genes, he moved to the European Molecular Biology Laboratory (EMBL) in Heidelberg, Germany, for a postdoc in the lab of Peer Bork on computational analysis of environmental sequence data (metagenomics), where he was later promoted to scientist, focusing on the integration of heterogeneous environmental “omics” data. The Raes lab combines large-scale, next-generation sequencing with novel computational approaches to investigate the functioning and variability of the healthy human microbiome at the systems level and study its alteration in disease.

Liping Zhao, Ph.D., is a Professor of Microbiology at the School of Life Sciences and Biotechnology at the Shanghai Jiao Tong University. His research focuses on the discovery and development of reusable software patterns, symmetries and models, and the application of these fundamentals to model-driven development and service-oriented computing. Zhao cofounded and led the first academic network on service science in the United Kingdom (http://www.ssmenetuk.org/) and acted as a guest editor for a special journal issue on Knowledge Intensive Service Systems for the International Journal of Services Technology and Management, and a book on Case Studies for Service Innovation. He has also received three IBM Faculty Awards for his contribution to software patterns’ research and edu-
cation. Zhao is a senior editor for *The ISME Journal* and is a Fellow of the American Academy of Microbiology.

**Eukaryotic Cell® To Merge into New Open-Access Journal, *mSphere™***

To leverage the broader reach of *mSphere*, *Eukaryotic Cell®* (EC) will join the new journal at launch. EC Editor in Chief Aaron Mitchell will serve as a Senior Editor of *mSphere*. Eight of the current EC editors also will join the new journal to handle peer-review of research on eukaryotic microbes. The launch of *mSphere* will offer the EC community a tremendous opportunity to expand the impact of their research. Mitchell and *mSphere* Editor in Chief Michael Imperiale will work together closely to ensure the needs of the EC community continue to be addressed at the new journal. ASM encourages EC authors to submit their research to *mSphere*.

**Bench Scientists Recognized at asm2015**

Nine young clinical laboratory scientists were recognized at asm2015 for their enthusiasm and commitment to the clinical microbiology profession. The recipients were awarded professional development grants to help facilitate their attendance at asm2015. Funding was generously provided by Accelerate Diagnostics, BD Diagnostics, Biofire, bioMérieux, COPAN Diagnostics Inc., Evergreen Scientific, GenMark Diagnostics Inc., Luminex, Medical Chemical Corporation, Nanosphere, OpGen, TECHLAB, TIB MOLBIOL, and ASM.

“Keeping up with the advancing technology and research in the field of microbiology is a must, so attending asm2015 enhanced my knowledge in the field and motivated me to keep up with up and coming advancements,” says Abigail Cunanan, MLS(ASCP), a 2015 recipient.

Initiated by the Clinical Microbiology Mentoring Committee (CMMC), the grants provided an opportunity for the recipients to interact with preassigned mentors, attend symposia, visit poster sessions, peruse industry-sponsored exhibits featuring the latest technological advances, and learn more about the profession of microbiology. To be eligible for the grant, applicants must be ASM members, have less than five years of clinical laboratory experience, be nondoctoral bench-level clinical microbiologists, never have attended an ASM General Meeting, and not be presenting a poster or talk at asm2015.

“Besides the number of new techniques and strategies I am able to bring home, I have also returned with a newfound desire to advance my career. I honestly had no idea where a career in clinical microbiology could take me,” says John Ford, MLS(ASCP), another 2015 recipient.

CMMC Chair Janet Hindler, MCLS, MT(ASCP), says “There is a compelling need to identify and support promising young professionals who embody the future of clinical microbiology. The challenge of combating infectious diseases is unrelenting, and will remain so in the years ahead. We need dedicated, creative, and energized people on the front lines who are focused on...”

**New AAC Section**

In response to the rise in antibiotic resistance, *Antimicrobial Agents and Chemotherapy* (AAC) has launched a new section, Challenging Clinical Cases in Antimicrobial Resistance (CCCAR). CCCARs are brief articles designed to familiarize and provide guidance to the reader on the clinical approach to the treatment of real, challenging cases involving multidrug-resistant organisms (bacteria, viruses [excluding HIV], fungi, and parasites). Cesar Arias and Lou Rice introduce the new section in an editorial (http://dx.doi.org/10.1128/AAC.01138-15).

CCCARs present a real case involving a multidrug-resistant organism, the case authors’ therapeutic strategy, and an expert clinician’s commentary. Only highly interesting cases that have important mechanistic and epidemiological or novel microbiological insights will be selected for review. All Challenging Clinical Case articles are made freely available at the time of publication.

The first case focuses on the challenge that carbapenem-resistant Enterobacteriaceae (CRE) may pose to the effective treatment of common infections in obstetric patients. Online commenting is available to encourage dialog.
improving the ways we process, analyze, and report results from diagnostic specimens. Immersing those prospective leaders now in the abundance of scientific information and networking opportunities available at asm2015 is an excellent step forward for their careers and our profession.”

“I met many people who gave me useful career advice and suggestions that I plan to use. A few of the conversations sparked ideas in me that I plan to use for future research projects both for work and in graduate school,” says Melissa Olson, MLS(ASCP)CM, another 2015 recipient.

The 2015 grant recipients are:

Robert Bowden, University of Florida
Abigail Cunanan, Sentara Norfolk General Hospital
John Ford, United Regional Lab
Phillip Lansang, Kaiser Permanente S. CA Regional Lab
Melissa Olson, Johns Hopkins Hospital
Yvette Phillips, Good Samaritan Hospital Medical Center
Kristen Romero, Tri-Core Reference Lab
Megan Waller, Inova Health Systems/Johns Hopkins Medicine

Kayla Wieting, OSU Wexner Medical Center


Intel International Science and Engineering Fair

In May, ASM celebrated its 10th year as a sponsor of special awards at Intel’s 66th annual International Science and Engineering Fair (ISEF) in Pittsburgh, Pa. Led by Miriam Barlow (University of California, Merced), ASM judges—JoAnne Flynn, Neal DeLuca, and Yuan Chang—reviewed innovative research projects of students from around the world and selected 10 standout individuals to receive this year’s ASM Intel ISEF Awards.

ISEF is the world’s largest precollege science fair and aims to provide students with the opportunity to present their work to doctorate-level scientists as well as compete for prizes given in 17 different categories. In order to attend the ISEF meeting, students must first earn a top prize at one of the 454 ISEF-affiliated fairs. Each of ASM’s honorees receives a cash prize, a certificate, and a one-year student membership to ASM.

This year, Karissa Wang of Roy, Utah, won first place at ISEF for her project entitled “Suppression of Antimicrobial Resistance Using CRISPRs.” Wang used clustered regularly interspaced short palindromic repeats (CRISPR) to target the antibiotic resistance gene in methicillin-resistant *Staphylococcus-aureus* (MRSA).

“Once infected, MRSA is very difficult to get rid of,” she says, “because it is resistant to many traditional antibiotics such as methicillin and other penicillin-like antibiotics.” Wang used a CRISPR system that worked with the dCas9 enzyme. “Foreign genes,” she says, “possibly inserted by a virus or bacteriophage, are integrated into the host genome. By creating this ‘library’ of invader genes, the bacteria can then recognize and attack them if the same genes come in again.” In the biotechnical field, these systems can be specially engineered to attack genes of our choosing. Wang applied this idea to MRSA by designing a CRISPR dCas9 system that targeted the *mecA* methicillin-resistant gene sequence. “Once transformed into MRSA,” she says, “the system was intended to suppress expression of *mecA*, leaving MRSA susceptible to methicillin.” Her tests showed that with this CRISPR system she was able to affect the susceptibility of MRSA to borderline between susceptible and resistant, a remarkable breakthrough in biotechnology and MRSA research.

Wang says she plans to build on her research: “I will continue modifying my experiment until I can get the MRSA to be completely susceptible,” she says. After that, she wants to look further into implementing a gene drive in to MRSA, an idea she came across in her CRISPR research. Since certain genes are more likely to be passed on than others, Wang wondered what would happen if she applied this to MRSA. “I would like to implement a gene drive in MRSA so that the CRISPR-dCas9 system is passed on,” she says, “even when the bacteria reproduce.” Finding such a way to introduce this gene into MRSA could potentially mean wiping out MRSA as a health concern.

Judge Miriam Barlow was very impressed with Wang’s project. “Karissa showed a lot of initiative in developing a novel method for combatting antibiotic resistance,” she says. “She independently developed the project, obtained funding

Olson
for it, and implemented cutting-edge technologies to successfully explore her hypothesis.”

Bernard Adriaan Smit, of Pretoria, South Africa, won second place with his project titled “Magnetotactic Bacteria with a Faraday Application,” and Matthew Dae-Young Park from Centreville, Va., took home third place with his project, “ Detecting Novel Strains of Lassa Virus via an Interdisciplinary Modernization Based on Genomic Sequencing.” The fourth-place winner was Carly Elizabeth Crump, who won for her project titled “Proteomic Characterization of Mosquito Host Cell Glycoproteins during Dengue Virus Egress.” The following six students earned fifth-place awards:

- Jeffrey Nathan Freidenson Bejar, “Determination of the Antimicrobial Activity of Heliotropium arboescens in Cultures of Bacteria that Cause Infection in the Respiratory Tract.”
- Brian Joseph Righter, “Designing a Genetic CRISPR-cas Detection Probe for Adherent Invasive Escherichia coli Utilizing Comparative Genomics.”
- Nicholas P. Miller, “Identification of a Crucial Legionnaire’s Disease Virulence Factor: The Transmembrane Permease Lpg0730 is Integral to the Ability of Legionella pneumophilia to Infect Protozoan Host Cells.”
- Rachel Johns, “The Medicinal Effects of J zuglone.”
- Rachel Danielle Swope, “Isolation of a Bacteriophage for Staphylococcus aureus from Rumen Fluid.”

For more information about Intel ISEF, please go to https://student.societyforscience.org/intel-isef

ASM Distinguished Lecturer Roster and Call for Nominations

The ASM Distinguished Lecturer (ASMDL) Program (formerly known as Waksman Foundation for Microbiology Lectures) annually selects a scientifically diverse group of lecturers who are available to speak at local ASM Branch meetings throughout the country. Lecturers are chosen through a competitive nomination process, and only the most distinguished lecturers and researchers are chosen to participate in the program.

Since its founding over 50 years ago, the ASMDL program has been a mainstay of Branch programming and has enhanced the scientific content available at the local and regional levels. The program reaches thousands of microbiologists, including students, every year and extends the reach and impact of ASM throughout the United States.

The ASM Distinguished Lecturer program gratefully acknowledges the full financial support currently provided by the ASM, as well as the past financial support provided by its original sponsor, the Waksman Foundation for Microbiology.

The ASM Distinguished Lecturer Committee is pleased to announce its 2015–2016 Roster:

- Thomas S. Alexander (Summa Health System, Akron, Ohio)
- Niaz Banaei (Stanford University, Palo Alto, Calif.)
- Briana M. Burton (Harvard University, Cambridge, Mass.)
- Ferric Fang (University of Washington School of Medicine, Seattle)
- Michael J. Federle (University of Illinois at Chicago)
- Ramon Gonzalez (Rice University, Houston, Tex.)
- Nancy D. Hanson (Creighton University, Omaha, Neb.)
A list of topic areas covered by each individual Lecturer can be found on the ASM website in the Network section at http://www.asm.org/distinguished-lecturer. For a list of upcoming ASM Branch meetings, go to www.asm.org/branches.

Call for Nominations. The ASM Distinguished Lecturer Committee will begin selecting speakers for the 2016–2018 program in November 2015. Nominations from the ASM Membership are welcome! For complete nomination procedures and speaker eligibility requirements, please visit our website: http://www.asm.org/distinguished-lecturer or e-mail adempsey@asmusa.org or membership@asmusa.org.

Deadline: The deadline for ASM Distinguished Lecturer nominations is 15 October 2015.

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ASM Public Affairs

ASM and APHL Draft HIV Western Blot White Paper

Members of the ASM Public and Scientific Affairs Board Laboratory Practices and Professional Affairs committees joined the Association of Public Health Laboratories (APHL) HIV and Viral Hepatitis Subcommittee to assist in preparation of “Limitations for the Use of HIV-1 Western Blot in Plasma/ Serum.” This document supports the discontinuation of HIV-1 Western blot testing in concert with the Centers for Disease Control and Prevention and APHL’s newly published laboratory algorithm for HIV diagnosis, “Laboratory Testing for the Diagnosis of HIV Infection: Updated Recommendations.” This document replaces previous HIV laboratory testing guidelines and is expected to help with earlier identification of HIV infections. See the ASM/APHL document at http://www.asm.org/images/PSAB/HIV-1-1-WesternBlotBrief.pdf for more details.

TJC Laboratory PTAC Selects ASM Member Vice Chair

ASM Public and Scientific Affairs Board Laboratory Practices committee member Yvette McCarter has been selected Vice Chair of the Joint Commission’s (TJC) Laboratory Professional and Technical Advisory Committee (Lab PTAC) and represented the ASM on a 23 June conference call. This committee is responsible for the development and refinement of standards and elements of performance in clinical laboratories. The Joint Commission accredits and certifies more than 20,500 health care organizations and programs in the United States and PTACs are an integral part of TJC’s advisory structure and represent the views of a diverse group of professional associations and other interests and by providing expert advice. To read more about Lab PTAC, go to http://www.jointcommission.org/accreditation/laboratory_ptac.aspx.

Former Professional Affairs Chair Invited to CMS Panel

The University of Tennessee Professor Vickie Baselski, former Chair of the ASM Public and Scientific Affairs Board Professional Affairs committee, has been invited to serve on the Centers for Medicare and Medicaid Advisory Panel on Clinical Diagnostic Laboratory Tests. The Panel was authorized by the Protecting Access to Medicare Act of 2014, enacted 1 April 2014, and is charged with providing expertise related to clinical diagnostic tests. One of the tasks the Panel will undertake is the establishment of payment rates for new clinical diagnostic laboratory tests.


ASM Staff Attends APUA Antibiotic Stewardship Seminar

The Alliance for the Prudent Use of Antibiotics (APUA) offered a webinar presented by Geraldine Hall entitled “Rapid Diagnostics in Clinical Microbiology as an Aid to Antibiotic Stewardship” on 16 June, which ASM staff attended. The seminar focused on a detailed explanation of rapid, nonculture identification methods and their unique role in antibiotic stewardship programs, improved patient outcomes, and lowered healthcare costs. APUA has been a leading global nongovernmental organization working to preserve the effectiveness of antibiotics for nearly 35 years. To read more about APUA and view the webinar materials, go to http://www.tufts.edu/med/apua/.

ASM Meetings and Conferences

ASM Microbe 2016: Advance Your Career at ASM Microbe 2016

Did you know that in addition to offering the high-quality scientific programming traditionally covered at the ASM General Meeting and ICAAC, the inaugural ASM Microbe 2016 (16–20 June 2016, Boston, Mass.) will also feature a brand-new track, the Profession of Microbiology (POM)? Entirely dedicated to your professional development, this new track will feature workshops and sessions relevant to all disciplines of the microbial sciences, such as communications, scientific writing, social media, research funding opportunities, and career choices from across the field of microbial science. To learn more about the POM track and the other tracks at this unique meeting, please visit www.asm.org/microbe2016.

2016 ASM Biodefense and Emerging Diseases Research Meeting: Abstract Submission Open Now. Submit your abstract before 29 October for the ASM Biodefense and Emerging Diseases Research Meeting (8–10 February 2016, Arlington, Va.), and you could get a chance to present your research in front of nearly 1,000 scientists, public health researchers, and policymakers! Don’t miss the opportunity to debut your research at this premier event focused on the collaborative efforts to manage bioterror agents, pathogens, and global surveillance. For more information, visit www.asm.org/biodefense2016.

Access ASM General Meeting Session Recordings Today. Unable to make it to this year’s ASM General Meeting in New Orleans? Attended the Meeting but missed a session? Watch session recordings from this event right from your desktop and stay up-to-date with the latest research findings in the field! Choose from three packages: General Program, Diagnostic Microbiology & Epidemiology Program, and All asm2015 Sessions (Save an additional 20%). Discounted rates are available to ASM members. For more information, visit www.asmeventsonline.com.

Upcoming ASM Conferences. ASM Conferences address the needs of
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ing for educators and researchers seeking to expand their networks, build their knowledge, and improve their teaching and research in microbiology and biology. With dozens of formal and informal opportunities to engage and learn, ASMCUE 2015 took place on 28–31 May in Austin, Tex.

Attended by approximately 400 participants from 15 difference countries, this ASMCUE was the largest and most diverse meeting yet. Forty-three percent of participants were first-time attendees, and a substantial number of future faculty took part in the meeting.

The ASMCUE Conference Planning Committee designed the meeting to focus "on the intersection of technology and education, while exploring scientific advances and pedagogical theory and practices," said Committee chair Laura B. Regassa (Georgia Southern University) in her post-meeting report.

Educational opportunities at the conference included science and education symposia; plenary, poster, and concurrent sessions; small group discussions; resource dissemination exhibits; networking opportunities;
product demonstrations; author signings; and more. Session themes incorporated “assessment tools and techniques, broadening participation, course-integrated undergraduate research, facilitating active learning, digital resources, non-traditional learning environments, professional development, quantitative biology, and teaching resources,” said Regassa.


The meeting’s education theme was featured in the session, “How We Can Be a Tool for Education Going and How Will We Get There?” This session featured education and medical development executives from Apple Inc., in an exploration of ways mobile technology affects higher education. In “Antibodies against Ebola Virus: the Road Map,” Erica Ollmann Saphire of the Scripps Research Institute shared insights from her research into the Ebola virus, particularly the progress of vaccine development. “The Role of Microbiology in Human Space Exploration: How NASA Can Be a Tool for Education and Research,” said Regassa.

Organized by the ASM Education Board Committee on Undergraduate Education, ASMCE is a leading annual meeting that advances the study and practice of education research in microbiology and biology. The ASMCE 2015 Conference Planning Committee consisted of Laura B. Regassa (chair) of Georgia Southern University, Naomi L.B. Wernick of the University of Massachusetts–Lowell (vice chair), Ned Barden of MCPHS University, Lee Hughes of the University of North Texas, Shelley M. Payne of the University of Texas at Austin, and Robyn A. Puffenbarger of Bridgewater College.

Planning is under way for the ASMCE 2016 program. Watch www.asmceu.org for updates.

National Registry of Certified Microbiologists

NRCM Welcomes 48 New Registrants

The National Registry of Certified Microbiologists (NRCM) certified 47 new Registrants in June 2015. The NRCM certifies microbiologists at every education- and career-level and administers examinations at testing centers worldwide in biological safety, food safety and quality, and pharmaceutical and medical device.

Certification is a tangible credential that documents your abilities and tells employers you are tested and proven. It’s a great way to stand out among similarly trained colleagues and gain distinction in the laboratory and profession. Isn’t it time you certified your worth? Learn more and apply today at www.asm.org/nrcm.

RM: Food Safety and Quality

Alani Barajas, B.S., Hardy Diagnostics, Santa Maria, Calif.


RM: Pharmaceutical and Medical Device

Kelly Allgood, B.S., CryoLife, Kennesaw, Ga.

Zachary S. Anderson, B.S., Nelson Laboratories, Inc., Taylorsville, Utah

Catherine Bailey, B.S., AmbioPharm, Inc., North Augusta, S.C.


Jeffrey Chuang, B.S., St. Jude Medical Center, Sylmar, Calif.


Jessi L. Done, B.S., UST Manufacturing LLC, Layton, Utah

Yolma Gonzalez, B.S., SHL Pharma, Deerfield Beach, Fla.

Dayra Gutierrez Alonso, B.S., Miami, Fla.

Mia Hanson, B.S., Tolmar, Inc., Fort Collins, Colo.


Lindy Johnson, B.S., WuXi AppTec, Atlanta, Ga.


Gayane Keshishyan, B.S., SGS Life Science Services, Chicago, Ill.

Phillip Kuether, B.S., CryoLife, Kennesaw, Ga.

Carly Manning, B.S., Chattem Inc., A Sanofi Company, Chattanooga, Tenn.

Adam Michaud, B.S., Nelson Laboratories, Salt Lake City, Utah

Stormy Miller, B.S., CryoLife, Kennesaw, Ga.

Emily Moffett, B.S., Tolmar, Fort Collins, Colo.

George Motoc, B.S., Tolmar, Inc., Fort Collins, Colo.
Lauren O’Keefe, B.S., WuXi AppTec, Inc., Atlanta, Ga.
Thomas K. Pace, B.S., Nelson Laboratories, Salt Lake City, Utah
Jason Ramer, B.S., Tolmar, Inc., Fort Collins, Colo.
Shazia A. Siddiqui, M.S., NAMSA, Irvine, Calif.
Mikki Skubal, B.S., SAFC Biosciences, Lenexa, Kans.
Brian Smith, B.S., Highpower Validation & Lab Services, Rochester, N.Y.
Adam Staples, B.S., Nelson Laboratories, Inc., Taylorsville, Utah
Justin Tettenborn, B.S., W.L. Gore and Associates-Flagstaff Medical Division, Ariz.
Angela Whiddon, B.S., Cryolife, Kennesaw, Ga.
SM: Biological Safety
Sharon E. Altmann, Ph.D., MRI-Global, Frederick, Md.
Jessica R. Bourquin, Ph.D., Texas A&M University, College Station
Patrick Conley, B.S., University of Texas Southwestern Medical Center-Environmental Health and Safety, Dallas
Colleen O. Driskill, B.S., University of Massachusetts Medical School, Worcester
Javier P. Fernandez, M.S., San Jacinto, Calif.
Jessica McCormick-Ell, Ph.D., Ph. D., Rutgers, the State University of New Jersey, Newark
Shirly Mildiner-Earley, Ph.D., University of Pennsylvania, Philadelphia
Lauriane Quenee, Ph.D., The University of Chicago, Argonne, Ill.
Anne Sallee, M.S., Massachusetts General Hospital, Boston
Tyler Stuart, B.S., Seattle Children’s Research Institute, Wash.

Lisa van Duin, M.S., The University of Melbourne, Victoria, Australia
Zachary R. Wilson, M.S., University of Colorado, Anschutz Medical Campus, Denver
SM: Pharmaceutical and Medical Device

International Affairs

Improving Microbiology Laboratory Services in Mozambique

Mozambique is a vast country with a recognized HIV and AIDS epidemic; with a prevalence of 11.5% among adults between 15–49 years, Mozambique is facing a generalized epidemic (WHO, Regional Office for Africa, Mozambique, http://www.afro.who.int/en/mozambique/country-programmes/disease-prevention-and-control/hivaid.html). Since 2008, ASM has been working in collaboration with local partners to address the country’s immediate laboratory testing capacity and quality improvement needs at the national and regional levels.

ASM has helped established the country’s immediate laboratory testing capacity and quality improvement needs; the assessment results showed weak diagnostic capacity to support patient care due mainly to the lack of essential equipment and supplies and lab accreditation to ensure quality standards at testing facilities.

At the end of the meeting, participants reached consensus on a draft microbiology test menu and testing algorithms, as well as on the standardization and harmonization of microbiology test supplies and equipment required for each laboratory tier within the laboratory network. With these next steps in mind, ASM will continue to assist DNAM and the MWG to ensure a well-executed plan to standardize microbiology laboratory services across the country.

Development of this publication was supported by Cooperative Agreement Number 5U2GGH001116–02 from the Department of Health and Human Services/Centers for Disease Control and Prevention, Center for Global Health, Division of Global HIV/AIDS. The contents of this article are solely the responsibility of the authors and do not necessarily represent the official views of the CDC.
Branches: ASM Activity at the Local Level

Theobald Smith Society, New Jersey Branch of ASM, and the Rutgers University ASM Student Chapter

The Theobald Smith Society (TSS) New Jersey Branch of ASM, in conjunction with the ASM Student Chapter at Rutgers University recently held the 2015 “Meeting in Miniature” and “62nd Selman A. Waksman Honorary Lectureship” at Rutgers University in New Brunswick, N.J. The 30 April event brought together students from Rutgers, Monmouth University, Princeton University, and the New Jersey Institute of Technology. Over 80 attendees thronged the poster session, a bevy of activity with 43 posters presented by undergraduates, graduates, and post-doctoral scientists. The crowd was treated to seven oral presentations from advanced graduate students and postdocs from both Rutgers and Princeton University. The Young Investigator Award was presented to Alexander Ploss of Princeton University, and the Graduate Scholarship recipient was Samantha Lee, a Ph.D. candidate at Rutgers. The highlight of the evening was the Waksman Honorary Lecture given by Barry N. Kreiswirth (Director, Public Health Research Institute, Rutgers University–Newark). Kreiswirth’s presentation, “Streptomycin Resistance to XDR Tuberculosis: Dr. Waksman Would Not Be Impressed,” was very well-received. Finally, recognition awards were given to Andrew Marinucci for his dedication to TSS as NJ State Science Fair judge, a Branch program developer, treasurer, and webmaster, as well as to Joyce Kohler for her service as the Branch membership coordinator and newsletter editor.

Dr. Waksman would have been impressed by these Theobald Smith Society activities! For more information on the TSS New Jersey Branch, see http://www.asmbranches.org/brnj/.

Nicole Lloyd
Ann Charles
Co-Presidents, Rutgers University ASM Student Chapter

Learn about microbiology career opportunities!

Invite an ASM speaker to your next Student Chapter meeting!

The Speakers’ Bureau currently features experts in areas such as biosafety, clinical microbiology and immunology, dairy, food safety, medical device, pharmaceuticals, and public health, and they want to talk to ASM students about their dynamic careers in microbiology.

Hear first-hand from speakers who have contributed to microbiome projects and biosecurity planning and chat with outbreak responders about curious cases!

If you are interested in hosting a live, recorded or video call presentation, visit http://bit.ly/ASMspeakers.
Microbe Mentor

How can I make myself more marketable for a career in Clinical Microbiology?

There are many excellent reasons to consider a career in the clinical field: great salaries and job security, job portability, chance to use state-of-the-art equipment—not to mention that your work improves patient health and saves lives. To provide you with the essentials for working in clinical microbiology, Microbe Mentor asked Janet Hindler, MCLS MT (ASCP), to give her thoughts on this thriving and in-demand field. She replied:

The first step would be to familiarize yourself with the work performed in a clinical microbiology laboratory. Most clinical microbiologists would be pleased to have you visit their laboratory, so get in touch with them and ask to visit. While you’re there, ask questions and show them that you are engaged in the laboratory’s activities. Demonstrating a high level of enthusiasm and professional curiosity goes a long way toward making you memorable and marketable for any future opportunities. There may even be an opportunity now for you to volunteer; if so, jump at the chance! That’s a surefire way to show your sense of commitment and learn more about the work.

But before your visit, do a little homework. Get an idea of what to expect so you can prepare your list of questions. The “Explore the Professions Tab” of the Clinmicro Portal contains short videos shot in clinical microbiology laboratories. You’ll find a wealth of useful and helpful information on this portal related to careers in clinical microbiology: clinmicro.asm.org/what-a-clinical-microbiologist-does

Next, you must know about the educational and certification requirements for positions in clinical microbiology.

Educational requirements. Most clinical microbiology laboratories employ individuals from all academic backgrounds. Those with associate or bachelor’s degrees usually work “on the bench” performing diagnostic tests, while those with master’s degrees would be more likely to have an administrative or technical specialist role. Directors of larger clinical microbiology laboratories almost always have a doctoral degree.

Certification: non-doctoral level. Most states require certification to perform diagnostic testing, and many laboratories outside these states also require certification for employment. Specific undergraduate courses, a bachelor’s degree, and completion of a 12-month clinical laboratory scientist (CLS) training program would allow you to sit for the certification exam administered by the American Society for Clinical Pathology (ASCP). Although most training programs encompass all types of diagnostic testing including clinical microbiology, a few focus specifically on clinical microbiology. These programs only offer certification for work in clinical microbiology. If preferred, you can sit for the clinical microbiology exam only, regardless of the training program taken. ASM partners with ASCP for the clinical microbiology certification program. There are other training and certification programs at the associate degree level also.

Certification: doctoral level. If you have a doctoral degree you might consider an ASM Committee on Postgraduate Education Program (CPEP), which is a two year postdoctoral fellowship program. CPEP prepares you to direct a clinical microbiology laboratory and would allow you to sit for ASM’s American Board of Medical Microbiology (ABMM) certification exam. Although the CPEP fellowship is not essential to sit for the exam, it does provide an increased likelihood of successful completion of that exam.

Knowledge and skills. Just as important as coursework and certification are the so-called “soft” skills and behaviors that can be developed in any microbiology laboratory and then brought into the clinical setting: strong organizational skills; the ability to work with precision; and a tight focus on details. There is little room for error when analyzing specimens from sick patients. It is also critical that you understand risks involved with handling pathogenic organisms and respecting safe practice rules. Yes, there are many rules when working in the health care field,
so make sure this would be something you could handle.

Finally, concerns related to infectious diseases and clinical microbiology such as antibiotic resistance, vaccines, and outbreaks due to contaminated food sources are receiving a lot of press these days. So ask yourself, “Do these stories excite me”? “Do I want to learn more about them”? “Do I want to help meet the challenges related to control of infectious diseases?” If you answer “yes” to these questions, then you may have what it takes for a career in the professionally satisfying and intellectually rewarding world of clinical microbiology.

For more information, please refer to ASM’s Clinical Microbiology Portal where you will find a brochure “Focus on Clinical Microbiology” and many other resources. http://clinmicro.asm.org/images/archive/Focus_on_CM_Careers.pdf.

Janet Hindler
Janet Hindler is a Senior Technical Specialist in Clinical Microbiology at UCLA Health. She holds an honorary doctoral degree from Albright College. Janet is Chair of the ASM Clinical Microbiology Mentoring Committee and a fellow in the American Academy of Microbiology. Her focus has been on antimicrobial susceptibility testing and she has taught and written extensively in this area.

Want to know more about Microbe Mentor and ASM career offerings? Sign up for the monthly notification list at microbementor@asmusa.org. Each message will include a sneak peek at the upcoming column, career and mentoring news, and more!
Application Deadlines

ABRCMS 2015: Accepting Abstracts and Travel Award Submissions  Exhibitor and attendee registration, abstract submissions, and travel award submissions are all open for the 2015 Annual Biomedical Research Conference for Minority Students (ABRCMS), set for 11-14 November in Seattle, Wash. This year marks the 15th anniversary for the conference, and attendees will benefit from a distinguished roster of speakers, along with numerous workshops, scientific presentations, professional development opportunities, networking events, and more. Students (undergraduate through graduate levels) are invited to submit abstracts and travel award applications for the conference. Travel awards are also available to (i) postdoctoral scientist and faculty members who serve as ABRCMS onsite presentation judges and (ii) faculty who wish to establish research partnerships and advance undergraduate research programs.

Deadlines are 1 September for the ASM LINK Undergraduate Faculty Research Initiative (UFRI) Fellowship, 11 September for ABRCMS Student Abstracts and Travel Awards, and 25 September for the ABRCMS Judges’ Travel Subsidy and the FASEB MARC Program Travel Award. For submission criteria, registration information, or program and speaker updates, visit www.abrcms.org. ABRCMS is managed by ASM and supported by the National Institute of General Medical Sciences of the National Institutes of Health under award number T36GM073777.

WWW: www.abrcms.org

Deadlines: 1 September, 11 September, and 25 September 2015 (see above).

ASM-IUSSTF INDO-US Professor in Microbiology  Sponsored by the Indo-US Science & Technology Forum and managed by ASM, this program offers two professorships with the intent to foster collaboration and scientific exchange between the United States and India. “Teaching Professorships” provide microbiologists in India and the United States with an opportunity to visit institutions in the other country to teach an interactive short course on a topic in any of the microbiological disciplines. “Research Professorships” provide support to microbiologist in India and the United States to conduct a novel research project in partnership with a colleague at a research facility in the other country. Applications should be submitted jointly by the prospective visiting professor and host.


Deadline: 15 December 2015.

National Registry of Certified Microbiologist (NRCM) Certification  The NRCM certifies microbiologist at the prebaccalaureate/baccalaureate, master’s and doctoral levels. Certification is offered in biological safety and quality; and pharmaceutical and medical device. Certification is offered in biological safety and quality; and pharmaceutical and medical device. Certification is offered in biological safety and quality; and pharmaceutical and medical device. NRCM certification is achieved by passing an online multiple-choice exam that is offered daily in the month of April at testing centers worldwide.

WWW: www.asm.org/nrcm

Deadline: 1 February 2016.

About Application Deadlines

The Application Deadlines section provides ASM members with information about certification programs, awards, and fellowships sponsored by ASM. More resources are available to members on the website at http://www.asm.org/index.php/awards-grants/whats-new-in-asm-awards-grants-fellowships-and-professorships.html. The website provides direct links to program Web pages for complete details, including eligibility requirements and application information.
ASM Meetings Calendar

8–12 September 2015.
ASM Conference on Pseudomonas 2015.
Washington, D.C.
WWW, http://conferences.asm.org/

17–21 September 2015.
ICAAC/ICC Meeting.
San Diego, Calif.

1st ASM Conference on Rapid Next-Generation Sequencing and Bioinformatic Pipelines for Enhanced Molecular Epidemiologic Investigation of Pathogens.
Washington, D.C.
WWW, http://conferences.asm.org/

24–29 October 2015.
7th ASM Conference on Biofilms.
Chicago, Ill.
WWW, http://conferences.asm.org/

2–5 November 2015.
Chicago, Ill.
WWW, http://conferences.asm.org/

13–17 April 2016.
13th ASM Conference on Candida and Candidiasis.
Seattle, Wash.
WWW, http://conferences.asm.org/

31 July–3 August 2016.
ASM Conference on Streptococcal Genetics.
Washington, D.C.
WWW, http://conferences.asm.org/

4–7 August 2016.
2nd ASM Conference on Experimental Microbial Evolution.
Washington, D.C.
WWW, http://conferences.asm.org/

9–12 September 2016.
6th ASM Conference on Beneficial Microbes.
Seattle, Wash.
WWW, http://conferences.asm.org/

ASM Conference on Infection and Cancer.
Washington, D.C.
WWW, http://conferences.asm.org/

11–14 December 2016.
ASM Conference on Antibacterial Development.
Washington, D.C.
WWW, http://conferences.asm.org/

About the Calendar

The ASM Meetings Calendar is provided as a service to readers of Microbe. It includes annual meetings and conferences organized by the Society. Detailed information for these events is published in the ASM Meetings and Conferences insert, which appears bimonthly in the center of Microbe.

As an added benefit of membership in ASM, an online calendar of microbiology-related meetings hosted by ASM and by other organizations is available through the ASM website. Any organization may submit items for the online calendar provided that submissions are of obvious interest to microbiologists. ASM will not permit announcements to appear in the calendar when the subject matter and dates conflict with ASM meetings or workshops. The calendar is located at https://info.asm.org/index.php/meeting-and-event-calendar. All entries in the online calendar are limited to conference name, dates, location, website, and contact information (person, address, telephone, fax, and/or e-mail). When websites and e-mail addresses are provided, links to them will be established. Because of the volume of submissions received, ASM staff is unable to provide proofs or other confirmation of receipt of each listing. Submit items for the online calendar through the “Add a new event/deadline” link on the Meeting and Event Calendar page.
Employment

POSITIONS AVAILABLE

Professor, Associate Professor, or Assistant Professor without Tenure

The Department of Laboratory Medicine, University of Washington, is recruiting a full-time Professor, Associate Professor, or Assistant Professor without tenure in clinical microbiology on the Clinician-Educator or Physician-Scientist pathway. This would be a 12-month, multi-year appointment. University of Washington faculty engage in teaching, research, and service. The primary service responsibility will be to participate in the direction of one or more of the Department’s clinical microbiology laboratories. Additional responsibilities include the teaching of residents, fellows, medical students, and medical laboratory scientist program undergraduates, and development of a suitable area of research or scholarship. Documented experience is required directing clinical laboratories and in the clinical interpretation of microbiological testing results. Applicants must have an M.D., D.O., Ph.D. or foreign equivalent and be board-certified or board-eligible in clinical or anatomic pathology by the American Board of Pathology, in clinical microbiology by the American Board of Medical Microbiology, or in infectious diseases by the American Boards of Internal Medicine or Pediatrics. In order to be eligible for University sponsorship for an H-1B visa, graduates of non-U.S. medical schools must show successful completion of all three steps of the U.S. Medical Licensing Exam (USMLE), or equivalent as determined by the Secretary of Health and Human Services. Salary will be commensurate with qualifications and experience. Applicants should submit CV, contact information for five references, and a brief statement of professional goals to Brad T. Cookson, M.D., Ph.D., c/o Karen Walter, Box 357110, University of Washington, Seattle, WA 98195-7110 (kwalter@uw.edu). The University of Washington is an affirmative action and equal opportunity employer. All qualified applicants will receive consideration for employment without regard to race, color, religion, sex, sexual orientation, gender identity, national origin, age, protected veteran or disabled status, or genetic information.

Employment Advertising

Microbe is published monthly and available to nearly 40,000 ASM members and institutional subscribers. Lead time for employment ads is about 3 weeks. Microbe is mailed around the 8th of the month of issue, but the delivery date is not guaranteed. Please consider delivery dates when setting application deadlines.

ASM does not accept classified advertisements that indicate a limitation, specification, or discrimination on the basis of race, religion, national origin, sex, mental or physical disability, age, or any other matters which may not be lawfully considered in making employment decisions. Employment notices that discriminate against microbiologists on the basis of a particular board certification or doctoral degree will not be accepted. Such advertisements will be rejected unless it can be established that the position by state or federal law or regulation requires a specific board certification or doctoral degree.

Classified

Classified ads must be typed, double spaced, with normal sentence capitalization (capital and lowercase letters). Microbe cannot accommodate requests for extra capitalization, boldface type, or other text or layout enhancements in classified ads.

Include the name and telephone and fax numbers of a contact person for questions about your ad copy. Incorrectly typed ads or ads with application deadlines earlier than the 15th of the publication month requested cannot be guaranteed placement in that issue.

Deadlines: Your ad must be received by the 1st of the month before the publication month to ensure timely publication (e.g., to appear in the November 2015 issue, your ad must be received by 1 October 2015).

Classified ads should be sent (with payment) to Walchli-Tauber Group, 2225 Old Emmorton Road, Suite 201, Bel Air, MD 21015, attn: Rhonda Beamer, tel. (443) 512-8899x106; fax, (443) 512-8909; e-mail, rhonda.beamer@wt-group.com.

Rates:

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Internet posting: All classified line advertising printed in Microbe also appears on the ASM website. Ads are posted to the website shortly before the issue mailing date and remain on the site for approximately 1 month. Hence, line ads placed for an issue of Microbe will be available to ASM website browsers around the beginning of the month and will overlap their print appearance in the magazine. All ads are replaced with the close of the next issue.

For display ad Internet posting costs, please contact Rhonda Beamer at the address given above.

Display

Display advertising closes the 1st of the month preceding publication. For specifications, rates, and deadlines for display ads, contact Rhonda Beamer at the address given above.
Join ASM Speakers’ Bureau!

Interested in sharing your microbiology or immunology career experience with ASM Student Chapters? ASM is looking for members employed in the clinical lab or industry, such as —

- Bioremediation
- Biosafety
- Biotechnology
- Dairy
- Food Safety
- Indoor Air Quality
- Medical Device
- Pharmaceuticals
- Policy
- Public Health
- Tech Sales
- Water Quality

The Speakers’ Bureau is designed to attract students to microbiology career opportunities. Speakers share with ASM Student Chapters information about their careers, how they got started and tips for success. Speakers can give a live, recorded or video call presentation!

ASM Members can visit http://bit.ly/ASMspeakers to learn more and sign up!

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Looking for jobs in microbiology?

Find Your Future at ASM Career Connections

Job Hunting? Visit ASM’s Online Jobs Website
Finding that new job just got a little easier. ASM Career Connections is the go to source for jobs in all areas of microbiology -- academia, clinical, industry, government, and more. Find your future today.

www.ASMCareerConnections.org
Small Things Considered

Death by Special Delivery
by Merry Youle

In the course of time, bacteria have opportunities to incorporate phage genes into their genomes. Frequently these genes originated in a temperate phage that integrated its DNA into the host’s chromosome and then was stranded there by a mutation that inactivated its escape mechanism. Most of the prophage genes will accumulate mutations and degenerate into pseudogenes that are eventually eliminated. Currently useful genes, such as those that encode virulence factors, will be maintained. All are potentially valuable hand-me-downs, nonessential genes that the cell can tinker with and perhaps adapt to its own purposes.

Particularly useful have been co-opted phage tails with their ability to deliver nucleic acid and proteins into specific target cells. Modified tail components are found in bacterial type VI secretory systems and in the tailocins, a group of bacterial weapons that inject effector molecules into bacterial or eukaryotic cells. For example, the enterobacterium Serratia entomophila employs a tailocin when colonizing the larvae of a scarab beetle, Costelytra zealandica, commonly known as the New Zealand grass grub. Infection by pathogenic strains of S. entomophila causes the larvae to stop feeding within 48 h. These larvae persist for several months in a state of starvation, but eventually the bacteria, having colonized the hindgut, escape into the hemocoel. Larval death follows soon thereafter.

Cessation of larval feeding requires a cluster of 18 genes on a plasmid carried by these strains. Evidence, including the presence of a complete lysis cassette, suggested that this cluster represents the relic of a prophage: the antifeeding prophage (Afp). Five of those genes are evolutionarily related to genes that encode tail proteins in phage T4 and other Myoviruses. Another gene encodes a tail fiber protein from avian adenovirus, likely how this phage tail was adapted to recognize a eukaryotic cell. Homologs of 16 genes form a cluster on the chromosome of Photorhabdus asymbiotica. Expression of that cluster in E. coli yielded structured particles visually identified as Myovirus-like tailocins. This strongly suggested that the afp cluster also encodes a tailocin.

For regulation of tailocin production, the plasmid in S. entomophila encodes a transcriptional antiterminator of the RfaH family (AnfA1) just upstream of the afp cluster. These proteins regulate operon transcription by binding a short DNA sequence within or upstream of the affected genes. Experimentally expressing Anf1 in trans in S. entomophila induced production of Afp particles that, when viewed under the electron microscope, appeared to be typical Myovirus-like tailocins complete with a contractile sheath and tail fibers.

The researchers proposed a model to describe how S. entomophila, armed with its Afp, goes about killing the grass grubs. They suggested that upon arrival in a larva, expression of the transcription antiterminator is switched on in a subset of the infecting bacteria—the shock troops. This, in turn, “induces” the prophage relics in those bacteria to produce Afps. Cell lysis soon follows, thereby releasing the Afps to deliver their cargo of anti-insect effectors into larval cells. The sacrifice of the shock troops enables their surviving kin to colonize the gut. Verification of this scenario awaits further research, along with other intriguing questions such as how target cell recognition triggers effector injection, whether sheath contraction is involved, and whether any human pathogens might some day add a tailocin to their toolkit.

Merry is a phageophilic microbiology writer/editor living on the Big Island of Hawaii.

ANTIBODIES
FOR INFECTIOUS DISEASES

Editors: James E. Crowe, Jr., Professor, Pediatrics, Pathology, Microbiology and Immunology, Vanderbilt University, and Director, Vanderbilt Vaccine Center; Diana Boraschi, Research Director, National Research Council; Rino Rappuoli, Global Head of Vaccines Research, Novartis Vaccines and Diagnostics

Antibodies for Infectious Diseases

Provides a broad survey across important aspects for understanding mechanisms of immunity to infectious disease, including general features of antibodies and approaches to antibody discovery, individual chapters highlighting antibodies against particular pathogens, and state-of-the-art technical advances and expression systems.

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List Price: $150 | eChapter: $30

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**FOURTH EDITION**

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Publishing in August 2015; Full-color illustrations, Glossary, Index

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www.ASMscience.org
books@asmusa.org

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